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EVALUATION OF INFLUENZA VACCINE IN AN EXPLOSIVE EPIDEMIC OF MIXED ETIOLOGY

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A SERIES of studies of influenza and influenza-like disease, has been in continuous progress, at Fort Dix, N. J., since the fall of 1947. These studies, conducted under the auspices of the Commission on Influenza of the Armed Forces Epidemiological Board, have been carried out with the support of the Office of the Surgeon General, Department of the Army, in collaboration with the medical staff of this installation and with the active participation of the First U. S. Army Medical Laboratory. A considerable volume of information has been gathered in the course of these studies relating to the problem of vaccination against influenza and to the broader problem of the etiology of influenza-like respiratory disease.

It had been our intention to put together a continuous story for the period 1947 to 1954; however, it has not been possible to make a full report, and because of the current interest in the influenza problem we have summarized some observations made during one of the more severe outbreaks—the one that occurred in the winter of 1950 to 1951. Clinical studies carried out during this outbreak are being reported by Lerro, Rapalski, and Schmerer.[1]

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Studies referred to were supported by the Commission on Influenza, Armed Forces Epidemiological Board, Washington, D. C.

An outbreak of influenza that was part of a widespread prevalence in the United States and other countries, began rather suddenly at Fort Dix at the end of January 1951, and reached a peak after the middle of February. A comparison of the intensity of the Fort Dix experience with that of the First Army area, of which Fort Dix is a part, and that of all Army installations in the continental United States, is shown in figure 1. This chart illustrates the difference in the prevalence of respiratory dis-

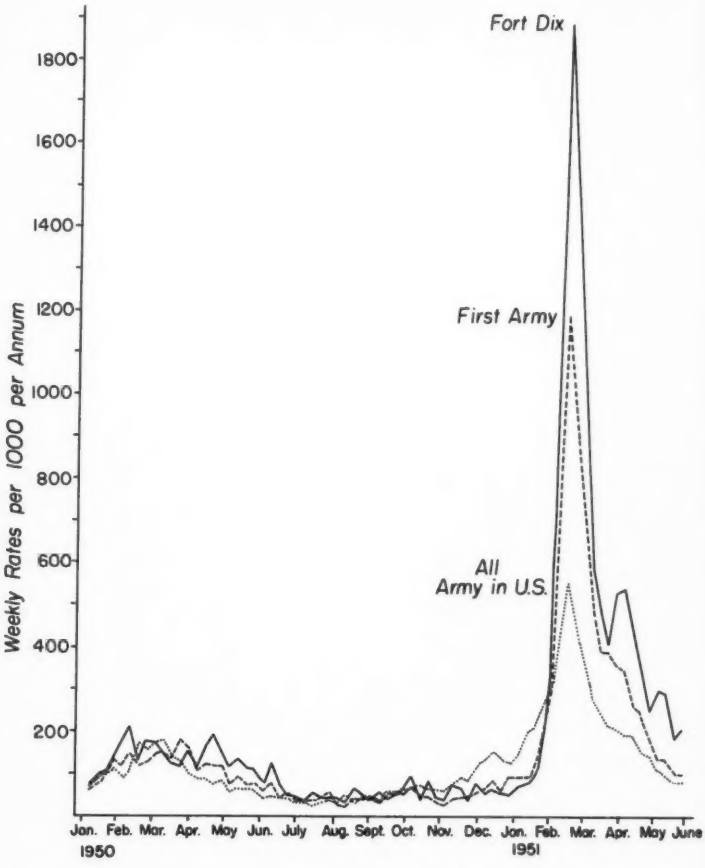

Figure 1. Hospital admissions for influenza and common respiratory disease, 1950-1951.

ease in corresponding periods of 1950 and 1951, and emphasizes the impact of the epidemic at this installation in comparison with an Army area command and with the Armed Forces in the

continental United States. The probable reason for the relatively greater severity of the outbreak at Fort Dix will become apparent from data to be presented. Nevertheless, the abruptness of the episode is clearly shown, and its force is evident from the number of cases that occurred in a relatively short period of time.

The daily admission rates for influenza and other acute respiratory diseases during this period, are shown graphically in figure 2, which reveals the fluctuations in admission rate, with week-end troughs followed by Monday peaks. These variations are not evident in the relatively smooth course of the epidemic curve described by the weekly admission rates (fig. 3). The columns in this figure compare the epidemic period of 1951 with the corresponding period of 1950 to show the excess morbidity resulting from the infectious agents prevalent in 1951.

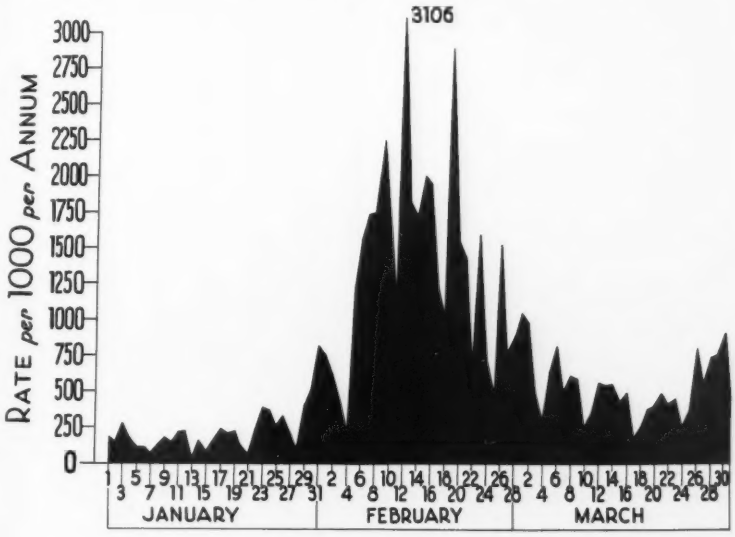

Figure 2. Daily admissions to U. S. Army hospital, for respiratory diseases, first quarter, 1951.

From the relative smoothness of the epidemic curve revealed in figures 1 and 3, it seemed reasonable to presume that a single etiologic agent was operative. That this was not the case was revealed in the course of studies on vaccination against influenza which were then in progress. These studies suggested that if a single etiologic agent was operative, and if the agent was an influenza virus, it was only remotely related antigenically to the antigen in the vaccine; alternatively, it was possible that more than one etiologic agent was in circulation.

An answer could be had because there were available for all admissions to hospital for respiratory disease, whether or not they were part of the vaccination studies, results of influenza-antibody determinations upon acute and convalescent serum samples. Analysis of the serologic data from almost 90

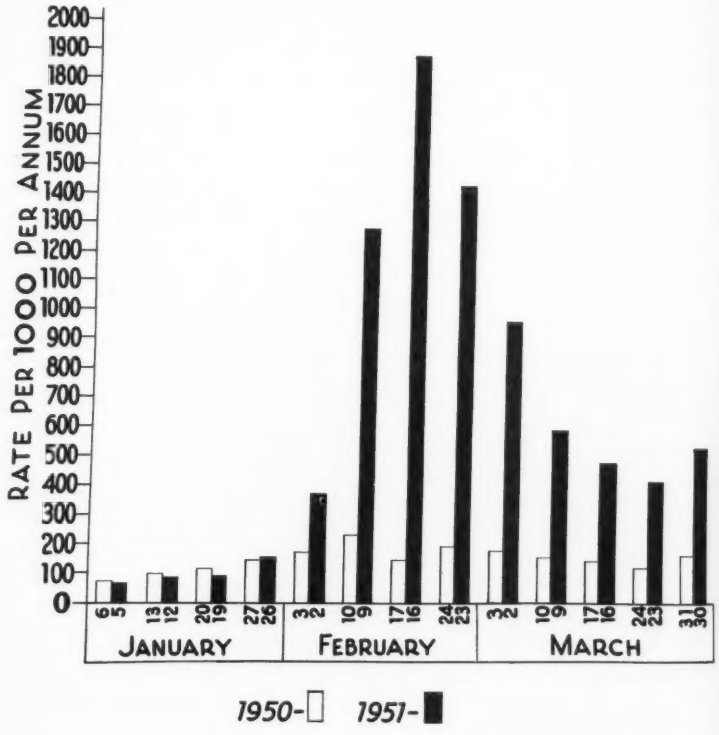

Figure 3. Weekly admission rates for respiratory diseases, Ft. Dix, N. J., first quarters of 1950 and 1951.

per cent of the admissions for respiratory disease during the period in question (table 1), suggested that two different etiologic entities were active almost concurrently, and produced the dramatic epidemic. The data in table 1 show that 88.6 per cent of the 3,841 admissions to hospital during January, February, and March 1951 were studied serologically, and that 91 per cent of the 2,401 admissions in February were so examined. Of the total group of 3,405 for whom serologic data were available, only 983 or 28.0 per cent were positive for influenza A, using 4-fold or greater increases in hemagglutination-inhibition antibody titer as index of positive reaction when acute and conva-

TABLE 1. *Results of serologic studies for influenza during outbreak at Fort Dix, N. J., in January to March, 1951*

Month	Proportion of cases studied serologically		Proportion serologically positive for influenza A	
	Number	Per cent	Number	Per cent
January	*234/344	68.0	**47/234	20.1
February	2186/2401	91.0	782/2186	35.8
March	985/1096	89.9	124/985	12.6
Total	3405/3841	88.6	983/3405	28.0

*Numerator = Number of cases studied serologically.
Denominator = Number of admissions for respiratory disease including influenza and all forms of common respiratory disease.

**Numerator = Number of cases positive for influenza A.
Denominator = Number of cases studied serologically.

lescent serum samples were tested simultaneously. The antigens used in the serologic test were PR8 and FMl. A group of negative and positive paired-serum samples were tested with the epidemic strain, and revealed no significantly increased sensitivity in diagnosis. Only 35.8 per cent of the 2,186 cases studied that occurred in February, and only 12.6 per cent of the 985 cases studied that occurred in March, were influenza A. The probable reason for the relatively low rates of serologically positive cases of influenza and for the disparity between the rates for February and March are suggested by an examination of figure 4.

The curves in figure 4 are derived from data on those cases in which paired acute and convalescent blood samples were available, and were constructed using the device of 7-day moving rates to smooth out the irregularities resulting from wide daily and week-end fluctuations in admissions. It is evident that a serologic diagnosis of influenza was made in a few cases in early January and a significant number at the end of January; then a sharp rise to a peak occurred prior to the middle of February, with an equally sharp decline, followed by a small number of scattered cases in March and April.

The curve describing the rate of occurrence of cases that were serologically negative for influenza reveals a rise beginning at about the same time as did the curve for influenza, but the rising limb of the curve was a trifle more gradual and reached a peak approximately 15 days after the influenza peak. The declining limb also seems to have been a bit more gradual than for the influenza curve, and there occurred a second wave in late

March and early April. These data suggest that another etiologic agent was operative in addition to the virus of influenza A and that it induced disease clinically indistinguishable from influenza A.[1]

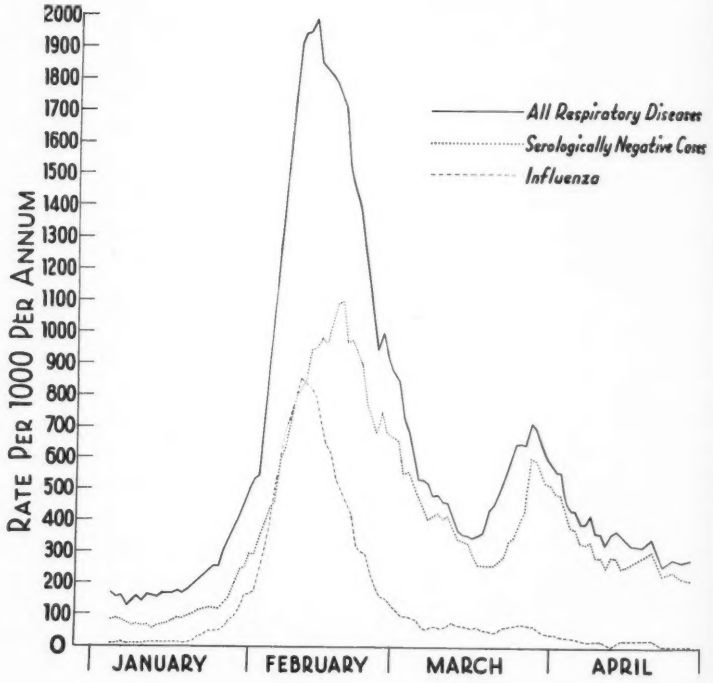

Figure 4. Seven-day moving rates, admissions to hospital, first quarter, 1951, for respiratory diseases, influenza, and influenza-like syndrome.

Although attempts were made by inoculation of chick embryos, suckling mice, and other animals to identify the presence of an agent other than influenza virus, no attempt was made to isolate a virus by tissue-culture methods. Subsequently, Hilleman and co-workers[2] and Rowe and associates,[3] using tissue cultures, identified the agents now included in the adenovirus group. Although we would have liked to have been able to report that one or more of the adenoviruses was responsible for the cases that could not be identified as having been caused by the influenza virus, it is not possible to do so because the material collected from the Fort Dix outbreak has not yet been restudied from this point of view.

The absence of this information has been responsible, in part, for the delay in making this report; however, the information

available is of interest even in the absence of a specific answer to this question, because there is strong circumstantial reason for believing that the adenoviruses, or agents that behave like them, contributed to the pattern observed. It was noted that the cases that were serologically negative for influenza occurred principally among new recruits, as is characteristic of adenovirus disease in military installations, whereas influenza virus disease was fairly widely distributed, both among new recruits and seasoned troops. Among 685 unvaccinated trainees admitted to hospital during the outbreak, 269 were diagnosed serologically as influenza A, and 416 were negative in this respect; among 600 operating personnel who were admitted during the same period, the ratio was reversed, with 382 positive for influenza A and 278 negative. It is probable that the concurrent outbreak among recruits of a disease not caused by the influenza virus, contributed to the greater intensity of the "influenza" outbreak at Fort Dix, which was a recruit training center, as compared with the remainder of the First Army area and with the Army in the United States (fig. 1).

The predominance of the noninfluenza virus disease among trainees is revealed further by comparison of the frequency of occurrence of influenza A and the influenza-like syndrome in trainee groups in which vaccination studies were carried out. In the vaccination program, by a method of random selection, one third of the population was given a type A virus vaccine, one third received a type B vaccine, and one third received a formalinized salt-solution preparation for control. The type A vaccine contained 500 CCA units per ml, and was comprised of equal parts of PR8, FM1, and the Cuppett strains. The type B vaccine also contained 500 CCA units, but was made up only of the LEE strain. The influenza viruses isolated from this outbreak were not greatly different antigenically from the Cuppett strain incorporated in the type A vaccine then under study.

The results of the vaccination studies are summarized in figure 5. Comparisons between vaccinated persons and controls are made separately for cases in which a diagnosis of influenza A was made serologically, and for cases of influenza-like disease that could not be shown by serologic methods to be caused by any of the known influenza viruses. There were approximately an equal number of cases of influenza A in the groups given type B vaccine (99 cases), and control material (96 cases). This is as expected. In the group given type A vaccine only, 26 cases were observed. This would suggest a degree of vaccine effectiveness of more than 70 per cent.

The significance of this is enhanced by the concurrent observations of distribution of vaccinated and controls among cases of respiratory disease that could *not* be diagnosed se-

rologically as influenza A. It is evident that the frequency of this illness was approximately the same in groups given type A vaccine, type B vaccine, or control material; therefore, influenza vaccine had no effect upon the incidence of this disease. However, it also is evident that the relatively lower incidence of influenza A in the type A vaccinated group is not an artifact due to the use of the criterion of serologic diagnosis, which could conceivably favor the vaccinated group. If the latter criticism applied, then one would have expected an excess in the type A column for the serologically negative cases.

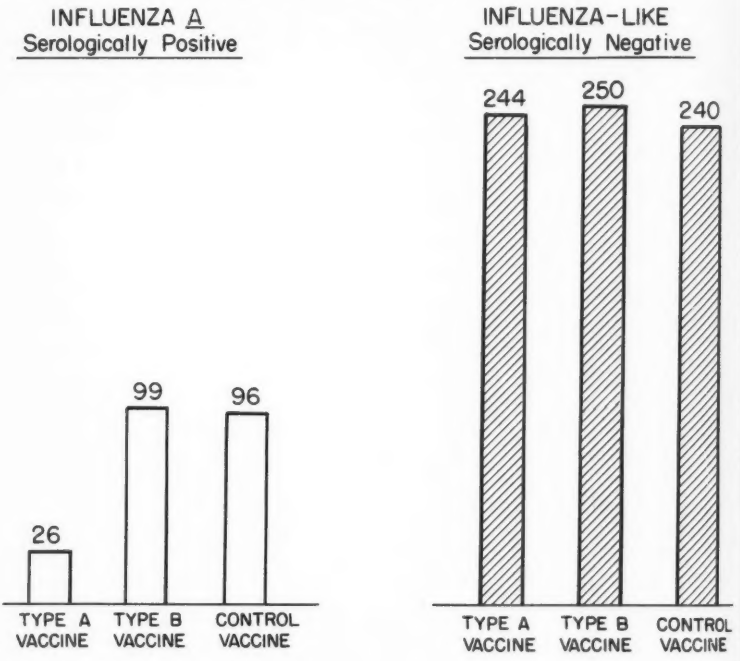

Figure 5. Distribution of cases of influenza A and of an influenza-like illness of undetermined cause in groups that had received either type A vaccine, type B vaccine, or a control inoculation.

It is clear that an evaluation of the efficacy of influenza vaccination without reference to the etiologic nature of the illness during the "presumably pure" influenza A epidemic of 1951 would have resulted in a conclusion of essentially no vaccine effect if the ratio of the combined heights of the two sets of columns were considered, whereas an analysis of the

effect of vaccine against the specific disease revealed more than 70 per cent effectiveness in prevention of influenza A.

DISCUSSION

Without the serologic data, one might have gained the impression that vaccination was essentially without effect, especially if the total number of influenza and influenza-like illnesses were indiscriminately considered together in attempting to evaluate the effectiveness of the vaccine.

There is little question from these data that the complete control of influenza and influenza-like illnesses, in military recruits at least, requires a combined vaccine that includes not only the influenza viruses but also those responsible for the clinically indistinguishable illnesses that can occur independently or simultaneously with influenza virus outbreaks. It is now possible to protect against the noninfluenza virus disease that is almost indistinguishable from it and caused by adenoviruses, since it has been demonstrated that vaccines for the prevention of such diseases are effective.[4]

The question of immunologic differences among strains of influenza virus is not yet fully resolved, and will not be until more years have gone by. Nevertheless, it would seem possible that stability of antigenic composition can begin to be approximated by including all strains, as may have occurred in the past, in an emulsified vaccine preparation.[5] It may be necessary to reinforce such basic immunization[6] and to add new strains to the vaccine, but this may be sufficient to reduce the extent to which small outbreaks become large, at least those outbreaks due to viruses related to the antigens present in such vaccines. While it is clear that protective measures have been devised for the control of influenza and adenovirus infections, all of our theoretical and technical knowledge is yet to be fully applied.

SUMMARY

Data are presented showing that a sharp outbreak of "influenza" at Fort Dix, N. J., in January, February, and March 1951, was caused by the almost simultaneous activity of influenza-A virus, and another etiologic agent that seems to have behaved like adenovirus in a recruit training center. During the height of the epidemic, only about one third of the cases were due to influenza-A virus infection. Evaluation of the efficacy of influenza vaccine based on clinical rather than serologic diagnosis would have resulted in the conclusion that the vaccine had essentially no effect, whereas in fact a single 1-ml dose of vaccine, containing 500 CCA units of the type A strains (PR8, FM1, and Cuppett) reduced by more than 70 per cent the frequency of hospital admissions for influenza A.

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THERAPEUTIC COMPARISON BETWEEN AUREOMYCIN AND APC IN CLINICAL INFLUENZA

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DURING an explosive epidemic of "influenza" at Fort Dix, N. J., in February 1951, 247 consecutively hospitalized patients were placed in a special study group in an attempt to resolve conflicting reports as to the efficacy of Aureomycin (brand of chlortetracycline) in the treatment of influenza.[1-3] This epidemic was found by Salk and Rapalski[4] to have been caused almost simultaneously by influenza-A virus and an agent that behaved like an adenovirus.

MATERIALS AND METHODS

From 6 to 10 February, the Admitting Officer of this hospital alternately placed patients admitted with clinical influenza in Study Groups A and B. When admissions to the study groups were closed, it was learned that the names of three patients admitted to Group A had been duplicated, and that of a total of 247 patients in the study, 122 were in Group A and 125 in Group B.

The patients in both groups were given yellow capsules of similar appearance four times a day. The contents of the capsules were not known to the ward medical officers or ward personnel, but were known to the Chief and Assistant Chief of the Medical Service and the hospital pharmacist, who distributed them to the wards in containers labeled "Flu Capsules A" and "Flu Capsules B." Capsules A, which were given to patients in Group A, contained 250 mg of Aureomycin. Capsules B, for patients in Group B, consisted of approximately 420 mg of APC powder (acetylsalicylic acid 200 mg, acetophenetidin 170 mg, and caffeine 50 mg). A margarine coloring agent was added to capsules B to give them the same appearance as capsules A.

From the Medical and Post Preventive Medicine Services, U. S. Army Hospital, Fort Dix, N. J., in collaboration with the Fort Dix Field Study of the Commission on Influenza, Armed Forces Epidemiological Board, under the supervision of Jonas E. Salk, M. D., University of Pittsburgh. Col. Lerro is now Senior Medical Advisor, U. S. Army Advisory Group, APO 102, San Francisco, Calif.

The patients were examined at least twice daily by the ward medical officers, and were seen once each night by the Chief and Assistant Chief of the Medical Service. Throat and sputum cultures, roentgenograms of the chest, blood counts, and determinations of cold agglutinins and erythrocyte sedimentation rates were obtained whenever possible for each case. If the patient developed unusually severe or untoward symptoms, he was dropped from the study group and given additional treatment as indicated. Patients developing complications were moved to a special ward for closer supervision and treatment.

OBSERVATIONS

As shown in table 1, 59 of the 247 cases originally admitted to the study were dropped either because they developed complications or inadvertently received other treatment, or because definite serologic data were not available. Of the 188 cases remaining in the study, 97 were in Group A and 91 in Group B.

TABLE 1. *Distribution of the 247 cases originally admitted to the study, and reasons for dropping 59 of these cases*

Reason dropped from study	Group A		Group B		Total	
	Number	Per cent	Number	Per cent	Number	Per cent
Developed complications	3	1.2	7	2.8	10	4.0
Given other treatment	2	0.8	13	5.3	15	6.1
Serologic data confused	4	1.6	3	1.2	7	2.8
Serologic date unavailable	16	6.4	11	4.2	27	10.9
Total dropped	25	10.1	34	13.7	59	23.8
Remaining in study	97	39.3	91	36.9	188	76.2
Originally in study	122	49.4	125	50.6	247	100.0

Three of the original 122 cases in Group A were dropped because of complications, two having developed otitis media on the third hospital day and one having been shown to have primary atypical pneumonia. Seven of the original 125 cases in Group B were dropped for complications. Three of these had primary atypical pneumonia (one also developing myocarditis subsequently), three had acute follicular tonsillitis, and one had otitis media on admission.

The fact that only 1.2 per cent of the group receiving Aureomycin were dropped because they developed complications, as compared with 2.8 per cent of the group receiving APC capsules, is interesting but not statistically significant. The Chi square

for this difference is 1.7706, or a P of slightly less than 0.2, and the observed difference could be ascribed to chance.

The 15 cases dropped from the study because they received other treatment included several treated by ward surgeons because of concern over hectic temperatures or suspicion of pneumonia, and two in which subsequent history revealed administration of antibiotics in the outpatient clinic during the 24-hour period prior to admission. The confused serologic data that caused the elimination of seven cases resulted from recent vaccinations for influenza.

Although influenza and the simultaneously occurring influenza-like syndrome could not be distinguished clinically, serologic studies (table 2) proved that of the 188 cases retained in the study 112 were influenza A, with exactly half of the proven cases in each of the two study groups. As shown in table 3, there was no significant difference in the distribution of maximum temperatures during the first five hospital days between the cases of serologically positive influenza A and those of the influenza-like syndrome.

TABLE 2. *Serologic findings on the 188 cases retained in the study*

Serologic finding	Group A		Group B		Total	
	Number	Per cent	Number	Per cent	Number	Per cent
Positive for Influenza A	56	29.8	56	29.8	112	59.6
Negative for Influenza A	41	21.8	35	18.6	76	40.4
Total	97	51.6	91	48.4	188	100.0

Data presented in table 4 show the mean numbers of days of illness prior to hospitalization, mean number of days of hospitalization, the per cent of the patients having a preceding history of upper respiratory infection, the per cent with acute onset, the mean maximum temperature in hospital, mean duration of fever in days, mean white blood cell count, and mean erythrocyte sedimentation rate. In neither influenza A nor in the influenza-like syndrome was there any significant effect to be noted between those treated with Aureomycin and those treated symptomatically with APC capsules.

The mean maximum temperatures for the first five days of hospitalization by treatment group for both diseases, as presented in table 5, shows no significant difference in the fever course of either treatment group. This is further illustrated in figure 1,

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TABLE 3. *Distribution of 188 uncomplicated cases by maximum temperatures, by day, first five hospital days*

Temperature (°F)	Total clinical influenza					Serologically positive influenza					Influenza-like syndrome				
	1st Day	2d Day	3d Day	4th Day	5th Day	1st Day	2d Day	3d Day	4th Day	5th Day	1st Day	2d Day	3d Day	4th Day	5th Day
	Number of cases														
97	1	4	8	23	19	1	4	3	11	10	0	0	5	12	9
98	0	15	35	57	79	0	11	22	36	50	0	4	13	21	29
99	15	51	68	71	65	9	28	41	43	35	6	23	27	28	30
100	23	42	36	23	13	16	25	21	11	9	7	17	15	12	4
101	44	24	18	7	2	23	15	10	5	1	21	9	8	2	1
102	59	24	14	1	2	33	13	8	1	0	26	11	6	0	2
103	30	16	5	2	0	17	7	3	1	0	13	9	2	1	0
104	8	7	0	0	0	7	5	0	0	0	1	2	0	0	0
105	2	1	0	0	0	2	0	0	0	0	0	1	0	0	0
106	1	0	0	0	0	0	0	0	0	0	1	0	0	0	0
Total	183	184	184	184	180	108	108	108	108	105	75	76	76	76	75
No record	5	4	4	4	8	4	4	4	4	7	1	0	0	0	1

TABLE 3. *Distribution of 188 uncomplicated cases by maximum temperatures, by day, first five hospital days*—Continued

Temperature (°F)	Total clinical influenza					Serologically positive influenza					Influenza-like syndrome				
	1st Day	2d Day	3d Day	4th Day	5th Day	1st Day	2d Day	3d Day	4th Day	5th Day	1st Day	2d Day	3d Day	4th Day	5th Day
	Per cent of cases														
97	0.5	2.2	4.3	12.5	10.6	0.9	3.7	2.8	10.2	9.5	0.0	0.0	6.6	15.8	12.0
98	0.0	8.2	19.0	31.0	43.9	0.0	10.2	20.4	33.3	47.6	0.0	5.3	17.1	27.6	38.7
99	8.2	27.7	37.0	38.6	36.1	8.3	25.9	38.0	39.8	33.3	8.0	30.3	35.5	36.9	40.0
100	12.6	22.8	19.6	12.5	7.2	14.8	23.2	19.4	10.2	8.6	9.3	22.4	19.8	15.8	5.3
101	24.1	13.0	9.8	3.8	1.1	21.3	13.9	9.2	4.7	1.0	28.0	11.8	10.5	2.6	1.3
102	32.2	13.0	7.6	0.5	1.1	30.6	12.0	7.4	0.9	0.0	34.7	14.5	7.9	0.0	2.7
103	16.4	8.8	2.7	1.1	0.0	15.7	6.5	2.8	0.9	0.0	17.4	11.8	.26	1.3	0.0
104	4.4	3.8	0.0	0.0	0.0	6.5	4.6	0.0	0.0	0.0	1.3	2.6	0.0	0.0	0.0
105	1.1	0.5	0.0	0.0	0.0	1.9	0.0	0.0	0.0	0.0	0.0	1.3	0.0	0.0	0.0
106	0.5	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	1.3	0.0	0.0	0.0	0.0
Total	100.0	100.0	100.0	100.0	100.0	100.0	100.0	100.0	100.0	100.0	100.0	100.0	100.0	100.0	100.0

TABLE 4. *Clinical characteristics of cases of influenza A and of influenza-like syndrome in the two treatment groups*

	Influenza serologically positive cases			Influenza-like serologically negative cases		
	Group A	Group B	Both groups	Group A	Group B	Both groups
Number of cases	56	56	112	41	35	76
Mean number of days of illness prior to hospital	2.3	1.6	1.9	1.8	2.0	1.9
Mean number of days of hospitalization	7.1	7.5	7.4	8.0	7.1	7.6
Per cent with preceding history of upper respiratory infection	46.4	35.7	41.1	34.2	51.4	42.1
Per cent with acute onset	73.2	71.4	72.3	87.2	80.0	81.6
Mean maximum temperature in hospital (°F)	101.8	101.7	101.7	102.1	101.3	101.7
Mean duration of fever days	2.6	2.9	2.7	2.7	2.4	2.6
Mean white blood cell count	8840	7736	8038	9462	8188	8859
Mean erythrocyte sedimentation rate (Wintrobe), mm/hour	9.2	12.9	11.1	11.1	10.6	10.5

TABLE 5. *Mean maximum temperatures in degrees Fahrenheit during first five days of hospitalization*

Hospital day	Influenza A		Influenza-like syndrome	
	Group A	Group B	Group A	Group B
1st	101.6	101.4	101.9	101.4
2d	100.5	99.0	100.6	100.3
3d	99.5	99.4	99.5	99.4
4th	98.8	98.7	98.7	98.7
5th	98.4	98.5	98.6	98.5

which shows the per cent of patients with maximum temperatures over 100°F on respective hospital days. Over 50 per cent of the patients in both groups no longer had temperatures of 100°F or more by the third hospital day.

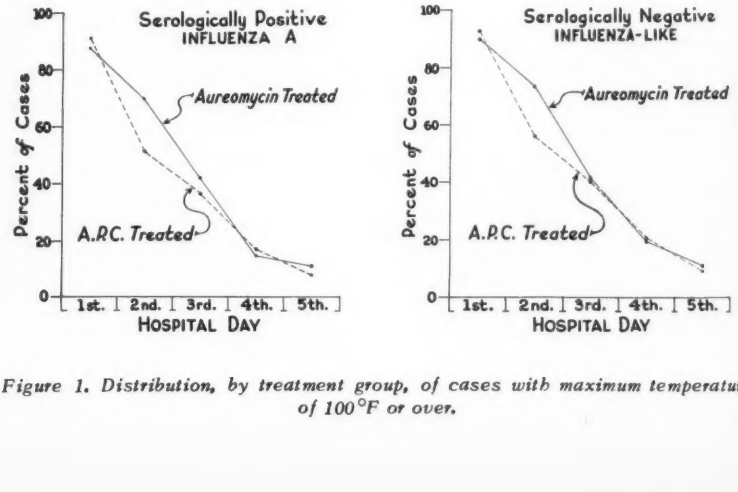

Figure 1. Distribution, by treatment group, of cases with maximum temperature of 100°F or over.

DISCUSSION

The data presented show that with the dosage of Aureomycin used in this study (250 mg four times a day) as compared with APC capsules (420 mg four times a day) there was no difference in the course of the two diseases, which appear to have been caused by different etiologic agents. The dosage of Aureomycin we employed was less than that used by Finland and co-workers[2] in their smaller series of cases, but was comparable to the dosage used by Thalmann and associates.[1]

The present study was limited originally to an evaluation of the effects of Aureomycin as compared to APC capsules in the treatment of uncomplicated clinical influenza. All patients in either of the study groups who developed pulmonary or other serious complications were dropped from the study. When the study was completed and the results of serologic tests for influenza became available, it was evident that we were dealing with two clinically indistinguishable disease entities, namely influenza A and an influenza-like syndrome.

Table 1 shows that of those cases retained in the study group, about 60 per cent were caused by an influenza-A virus. Although data as to the mean number of days of hospitalization are included, no conclusions based on these data should be made because these soldiers were discharged from the hospital only when they were fit for duty. All of the other data are significant, in that they show that neither with serologically positive influenza nor the influenza-like syndrome is there any appreciable difference between the treated groups for any of the categories listed.

SUMMARY

During a sharp outbreak of clinical influenza at an Army installation, 247 consecutively admitted cases were placed in a study group to determine the effectiveness of Aureomycin on clinical influenza. The 122 patients in Group A were treated with Aureomycin capsules, 250 mg four times a day. The 125 patients in Group B were treated with APC capsules containing acetylsalicylic acid, 200 mg; acetophenetidin, 170 mg; caffeine, 50 mg; and a yellow coloring agent. Any patient who developed complications or appeared to be acutely and severely ill was excluded from the study. For this and other reasons only 188 cases were retained in the study.

When the results of tests on acute and convalescent blood sera were reported, it was learned that we were dealing with two disease entities, namely influenza A and an influenza-like syndrome. In the latter disease the usual serologic tests for influenza and also virus isolation attempts were negative.

The results showed that in this series of cases Aureomycin in the dosage employed had no significant effect as contrasted with APC on the clinical course of uncomplicated proven influenza A and on the influenza-like syndrome.

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ARTIFICIAL RAIN MAKING

"Among the witch-doctor fraternity rainmaking is often an important activity, but it does not appear in the curriculum of the modern medical student. To that extent perhaps we must put it down as a lost medical art. However, it has engaged the attention of the physical scientists in recent years...

Artificial rainmaking is unlikely to be of economic importance unless methods are available which can be applied easily and cheaply on a wide scale. It is no use relying on methods which involve treatment of individual clouds. Silver iodide released from aircraft remains active at cloud level for several hours in daylight and for a much longer time at night. It can readily be dispersed over a very wide area. This provides a method which can be applied for practical rainmaking. At the same time the fact that silver iodide can successfully induce rain to fall from suitable cloud systems does not necessarily mean that there will be an increase of rainfall over an area if the process is repeated a large number of times. The possibility exists that in each case the clouds might have rained naturally if left alone for a little longer."

—EDITORIAL from "Current Comment"
in *Medical Journal of Australia*
pp. 60-61, July 13, 1957

UNUSUALLY SEVERE CASES SEEN IN AN EXPLOSIVE EPIDEMIC OF INFLUENZA AND INFLUENZA-LIKE SYNDROME

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AN acute epidemic of what appeared clinically to be influenza developed at Fort Dix, N. J., in the latter part of January 1951 and reached a sharp peak in February. Serologic studies reported by Salk and Rapalski[1] showed that the epidemic was of mixed etiology, being caused by the nearly simultaneous activity of influenza-A virus and an agent that behaved like one of the adenoviruses subsequently described by Hilleman[2] and Rowe[3] and their associates.

During the period 1 January through 31 March, more than 3,400 patients were admitted to the U. S. Army Hospital at Fort Dix. The vast majority showed only those symptoms usually seen in mild cases of influenza, including chills, fever, malaise, generalized aches and pains, sore throat, congested nares, persistent cough, profuse perspiration, and weakness. In these cases, the illness ran a short, febrile course followed by rapid and complete recovery. A small number of the patients, however, were severely ill, with various debilitating complications and prolonged convalescence.

In 0.88 per cent of the 3,400 cases there was pneumonia with delayed resolution despite adequate chemotherapy; in 0.12 per cent there was myocarditis, which often appeared late in the course of the illness or during convalescence. The following four cases illustrate these special features.

CASE REPORTS

Case 1. An 18-year-old man who had been ill since 20 January with "a common cold" was admitted to the hospital on 2 February because

From the Medical and Post Preventive Medicine Services, U. S. Army Hospital, Fort Dix, N. J., in collaboration with the Fort Dix Field Study of the Commission on Influenza, Armed Forces Epidemiological Board, under the supervision of Jonas E. Salk, M. D., University of Pittsburgh, Pittsburgh, Pa. Col. Lerro is now Senior Medical Advisor, U. S. Army Advisory Group, APO 102, San Francisco, Calif.

of acute illness and the finding of coarse rales throughout both lung fields. Physical examination on admission revealed dullness and numerous moist rales over the right lung field posteriorly and in the right axilla. The remainder of the admission findings and a summary of the complete course in the hospital are shown in figure 1.

This was a case of serologically proven influenza-A complicated by bilateral pneumonia, with a severe, prolonged, hectic, febrile course showing no response to multiple-antibiotic and sulfonamide therapy. There was delayed resolution of the pneumonia, and *Monilia albicans* was recovered from the sputum following the intensive use of antibiotics.

It is not possible to state with certainty that this was a bacterial pneumonia, despite the finding of pneumococci in the sputum. These organisms were not subjected to a Neufeld typing and may have represented a nonpathogenic variety of pneumococcus rather than one of the virulent strains. It is noteworthy that the patient's fever and pulmonary involvement were not influenced by extensive use of antibiotics resulting in suppression of the normal bacterial flora of the throat. This suggests that the influenza virus may have a severe, prolonged pathogenicity of its own, even if secondary invaders are suppressed; however, it is not possible to exclude the fact that moniliasis may have contributed to the patient's symptomatology in the latter phases of his illness. The employment of vigorous supportive measures such as oxygen therapy and maintenance of fluid balance, along with good nursing care, is shown to be of prime importance in the management of an illness of this type.

Case 2. A 22-year-old man who had been increasingly ill with what appeared to be mild influenza since 2 February was admitted to the hospital on 9 February with the symptoms listed under that date in figure 2. Shortly before admission he had developed vomiting, and some diarrhea. Figure 2 summarizes the complete hospital course.

In this case of serologically proven influenza-A complicated by bronchopneumonia, there was prolonged high fever, mental confusion and actual delirium, and eventual electrocardiographic findings compatible with myocarditis. There was no apparent response to antibiotics and sulfonamides. Occasional pneumococci were found in the sputum culture taken on admission, but none in the blood culture.

Case 3. A 22-year-old man was admitted to the hospital on 11 February for a respiratory condition of four days' duration. He appeared acutely ill and there was dullness and bronchial breathing over the right chest anteriorly. Figure 3 lists his symptoms on admission and presents a summary of his complete course while hospitalized.

This patient had serologically proven influenza-A, complicated by pneumococcic pneumonia as evidenced by lobar consolidation seen in roentgenograms of the chest, a high white blood cell count, and the presence of pneumococci in the blood stream. Despite intensive

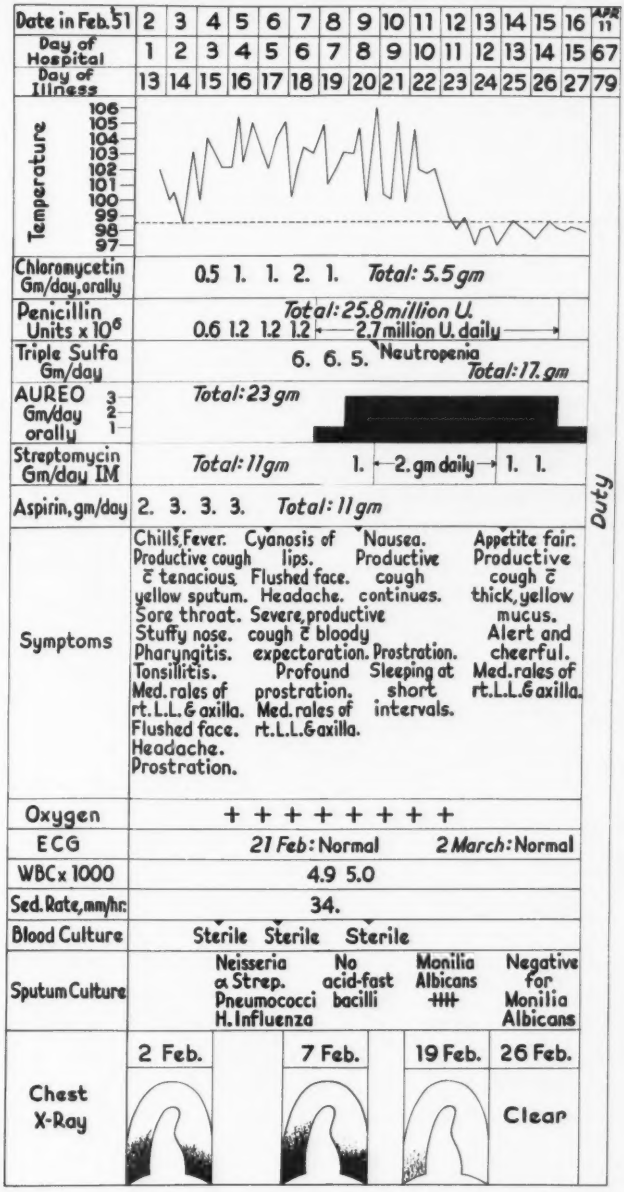
Date in Feb. 51
2 3 4 5 6 7 8 9 10 11 12 13 14 15 16
Apr 11
Day of Hospital
1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 67
Day of Illness
13 14 15 16 17 18 19 20 21 22 23 24 25 26 27 79
Temperature
106 105 104 103 102 101 100 99 98 97
Chloromycetin Gm/day, orally
0.5 1. 1. 2. 1. Total: 5.5 gm
Penicillin Units x 10⁶
Total: 25.8 million U.
0.6 1.2 1.2 1.2 2.7 million U. daily
Triple Sulfa Gm/day
6. 6. 5.
Neutropenia
Total: 17. gm
AUREO Gm/day orally
3 2 1
Total: 23 gm
Streptomycin Gm/day IM
Total: 11 gm
1. 2. gm daily 1. 1.
Aspirin, gm/day
2. 3. 3. 3. Total: 11 gm
Duty
Symptoms
Chills, Fever. Productive cough & tenacious yellow sputum. Sore throat. Stuffy nose. Pharyngitis. Tonsillitis. Med. rales of rt. L.L. & axilla. Flushed face. Headache. Prostration.
Cyanosis of lips. Flushed face. Headache. Severe, productive cough & bloody expectoration. Profound prostration. Med. rales of rt. L.L. & axilla.
Nausea. Productive cough continues. Prostration. Sleeping at short intervals.
Appetite fair. Productive cough & thick, yellow mucus. Alert and cheerful. Med. rales of rt. L.L. & axilla.
Oxygen
+ + + + + + + +
ECG
21 Feb: Normal
2 March: Normal
WBC x 1000
4.9 5.0
Sed. Rate, mm/hr.
34.
Blood Culture
Sterile Sterile Sterile
Sputum Culture
Neisseria & Strep. Pneumococci H. Influenza
No acid-fast bacilli
Monilia Albicans +++
Negative for Monilia Albicans
Chest X-Ray
2 Feb.
7 Feb.
19 Feb.
26 Feb.
Clear

Figure 1. Consolidated hospitalization chart; case 1, influenza A and bilateral pneumonia.

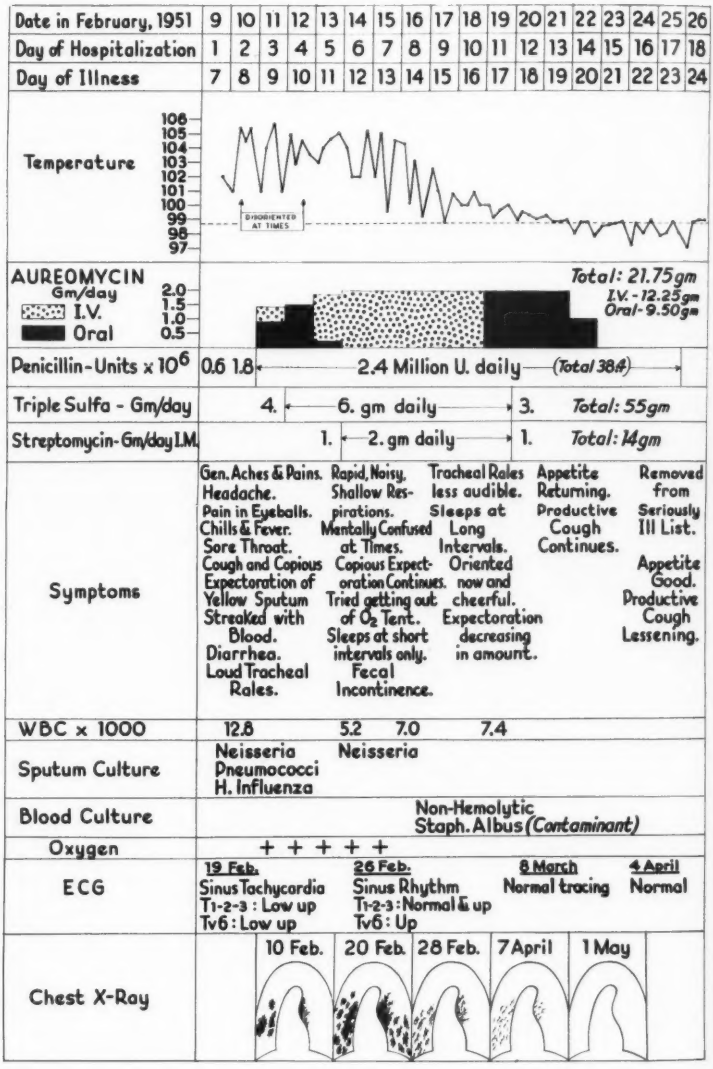
Date in February, 1951 9 10 11 12 13 14 15 16 17 18 19 20 21 22 23 24 25 26
Day of Hospitalization 1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18
Day of Illness 7 8 9 10 11 12 13 14 15 16 17 18 19 20 21 22 23 24
Temperature
106 105 104 103 102 101 100 99 98 97
DISORIENTED AT TIMES
AUREOMYCIN Gm/day
I.V.
Oral
2.0 1.5 1.0 0.5
Total: 21.75gm
I.V. - 12.25gm
Oral - 9.50gm
Penicillin-Units x 10^6
0.6 1.8
2.4 Million U. daily
(Total 38.4)
Triple Sulfa - Gm/day
4.
6. gm daily
3.
Total: 55gm
Streptomycin-Gm/day I.M.
1.
2. gm daily
1.
Total: 14gm
Symptoms
Gen. Aches & Pains. Headache. Pain in Eyeballs. Chills & Fever. Sore Throat. Cough and Copious Expectoration of Yellow Sputum Streaked with Blood. Diarrhea. Loud Tracheal Rales.
Rapid, Noisy, Shallow Respirations. Mentally Confused at Times. Copious Expectoration Continues. Tried getting out of O2 Tent. Sleeps at short intervals only. Fecal Incontinence.
Tracheal Rales less audible. Sleeps at Long Intervals. Oriented now and cheerful. Expectoration decreasing in amount.
Appetite Returning. Productive Cough Continues.
Removed from Seriously Ill List. Appetite Good. Productive Cough Lessening.
WBC x 1000
12.8 5.2 7.0 7.4
Sputum Culture
Neisseria Pneumococci H. Influenza
Neisseria
Blood Culture
Non-Hemolytic Staph. Albus (Contaminant)
Oxygen
+ + + + +
ECG
19 Feb. Sinus Tachycardia T1-2-3 : Low up Tv6 : Low up
26 Feb. Sinus Rhythm T1-2-3 : Normal & up Tv6 : Up
8 March Normal tracing
4 April Normal
Chest X-Ray
10 Feb. 20 Feb. 28 Feb. 7 April 1 May

Figure 2. Consolidated hospitalization chart; case 2, influenza A with bronchopneumonia and myocarditis.

antibiotic and triple sulfonamide therapy, the pneumonia did not resolve completely until the 60th day of illness, and some residual pleural thickening remained in the right costophrenic angle. Even in the presence of unresolved pneumonia, however, the patient had a normal temperature after the 13th day of his illness and was relatively symptom-free after the 30th day.

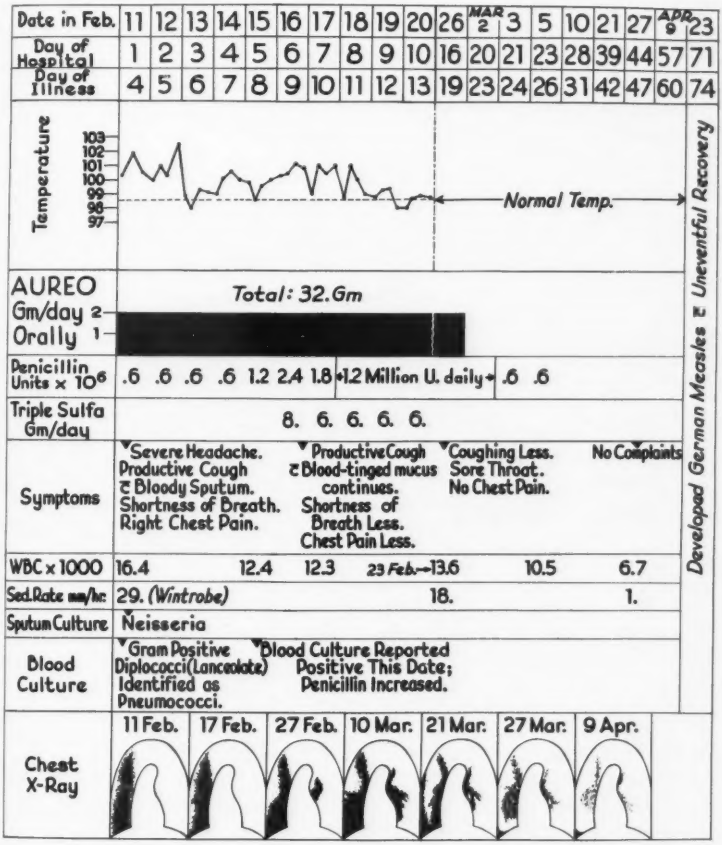
Date in Feb. 11 12 13 14 15 16 17 18 19 20 26 MAR 2 3 5 10 21 27 APR 9 23
Day of Hospital 1 2 3 4 5 6 7 8 9 10 16 20 21 23 28 39 44 57 71
Day of Illness 4 5 6 7 8 9 10 11 12 13 19 23 24 26 31 42 47 60 74
Temperature
103
102
101
100
99
98
97
Normal Temp.
AUREO
Gm/day 2
Orally 1
Total: 32.Gm
Penicillin Units x 10⁶
.6 .6 .6 .6 1.2 2.4 1.8 1.2 Million U. daily .6 .6
Triple Sulfa Gm/day
8. 6. 6. 6. 6.
Symptoms
Severe Headache. Productive Cough & Bloody Sputum. Shortness of Breath. Right Chest Pain.
Productive Cough & Blood-tinged mucus continues. Shortness of Breath Less. Chest Pain Less.
Coughing Less. Sore Throat. No Chest Pain.
No Complaints
WBC x 1000
16.4 12.4 12.3 23 Feb.—13.6 10.5 6.7
Sed. Rate mm/hr.
29. (Wintrobe) 18. 1.
Sputum Culture
Neisseria
Blood Culture
Gram Positive Diplococci (Lancelate) Identified as Pneumococci.
Blood Culture Reported Positive This Date; Penicillin Increased.
Developed German Measles & Uneventful Recovery
Chest X-Ray
11 Feb. 17 Feb. 27 Feb. 10 Mar. 21 Mar. 27 Mar. 9 Apr.

Figure 3. Consolidated hospitalization chart; case 3, influenza A and pneumococcic pneumonia.

Case 4. A 22-year-old man who had had malaise, fever, cough, and sore throat for three days was admitted to the hospital on 24 February with a temperature of 106.4°F. He was delirious and vomiting repeatedly. His pulse rate was 135 per minute and respiration was 30 per minute and shallow, but no abnormal signs were elicited on examination of the heart and lungs. A summary of the details of the

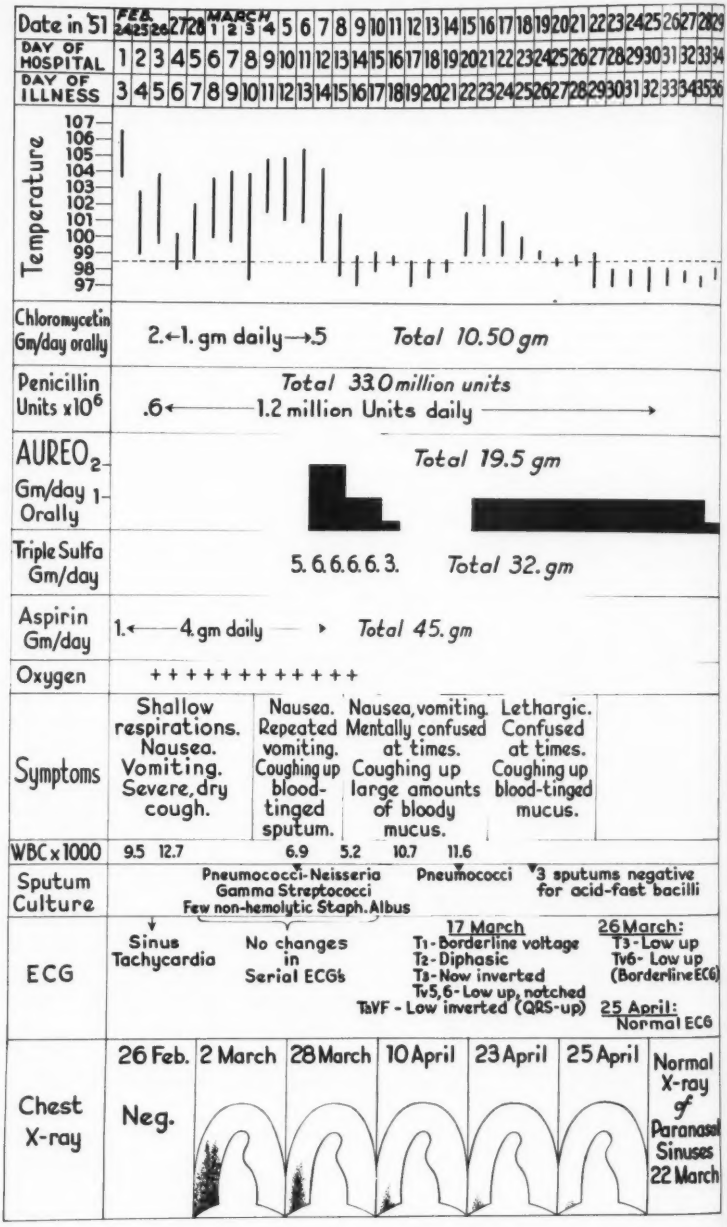
Date in '51
FEB. 24 25 26 27 28
MARCH 1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 20 21 22 23 24 25 26 27 28 29
DAY OF HOSPITAL 1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 20 21 22 23 24 25 26 27 28 29 30 31 32 33 34
DAY OF ILLNESS 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 20 21 22 23 24 25 26 27 28 29 30 31 32 33 34 35 36
Temperature
107 106 105 104 103 102 101 100 99 98 97
Chloromycetin Gm/day orally
2.←1. gm daily→.5 Total 10.50 gm
Penicillin Units x10⁶
Total 33.0 million units
.6← 1.2 million Units daily →
AUREO2 Gm/day 1 Orally
Total 19.5 gm
Triple Sulfa Gm/day
5. 6. 6. 6. 6. 3. Total 32. gm
Aspirin Gm/day
1.← 4 gm daily → Total 45. gm
Oxygen
+ + + + + + + + + + + + +
Symptoms
Shallow respirations. Nausea. Vomiting. Severe, dry cough.
Nausea. Repeated vomiting. Coughing up blood-tinged sputum.
Nausea, vomiting. Mentally confused at times. Coughing up large amounts of bloody mucus.
Lethargic. Confused at times. Coughing up blood-tinged mucus.
WBC x 1000
9.5 12.7 6.9 5.2 10.7 11.6
Sputum Culture
Pneumococci-Neisseria Gamma Streptococci Few non-hemolytic Staph. Albus
Pneumococci
3 sputums negative for acid-fast bacilli
ECG
Sinus Tachycardia
No changes in Serial ECGs
17 March
T1 - Borderline voltage
T2 - Diphasic
T3 - Now inverted
Tv5, 6 - Low up, notched
TaVF - Low inverted (QRS-up)
26 March:
T3 - Low up
Tv6 - Low up
(Borderline ECG)
25 April:
Normal ECG
Chest X-ray
26 Feb. Neg.
2 March
28 March
10 April
23 April
25 April
Normal X-ray of Paranasal Sinuses 22 March

Figure 4. Consolidated hospitalization chart; case 4, influenza-like syndrome with pneumonia and myocarditis.

course in hospital is presented in figure 4. Serologic study of acute and convalescent blood sera revealed no significant rise in antibody titer for influenza.

This patient had a severe influenza-like syndrome soon complicated by pneumonia and later by myocarditis. The pneumonia developed on the ninth day of illness, after four days of treatment with penicillin and Chloromycetin. Multiple-antibiotic and sulfonamide therapy had no clinically observable effect on either the influenza-like syndrome or the pneumonia, and pneumococci still could be recovered from the sputum after prolonged treatment with penicillin, Aureomycin, Chloromycetin, and triple sulfonamide. During the later stages of the patient's illness, there was electrocardiographic evidence of myocarditis as manifested by development of ST-T changes. This persisted for over a month, but was followed by complete recovery.

DISCUSSION

These four cases are representative of the relatively small number in which influenza A or the influenza-like syndrome assumed a severe and malignant form, or in which there were serious complications. To a variable extent, there was pulmonary infiltration with notably delayed resolution, prolonged hectic fever, severe prostration with impending circulatory collapse, and electrocardiographic evidence of myocarditis. Lymphadenopathy appeared in a large number of cases, and in an occasional case there was splenomegaly.

Myocarditis

This was an important though infrequent complication. A tachycardia while at rest in a patient (case 2) who was hospitalized early in the epidemic, caused us to re-examine his cardiovascular system. An electrocardiogram revealed ST-T wave changes compatible with myocarditis. It could not be determined when during the course of his illness this patient had developed the myocarditis, and after one week the ST-T waves returned to normal.

In view of this finding and of the report by Finland and associates[4] of two cases of influenza with post-mortem findings of acute nonbacterial myocarditis, we obtained electrocardiograms on all patients during the remainder of the epidemic who developed complications, had an unusual clinical course, or developed persistent tachycardia, particularly if it occurred late in the course of the illness or during convalescence.

Myocarditis also occurred with the influenza-like syndrome, as illustrated by case 4. This patient had a persistent tachycardia throughout his illness. Serial electrocardiograms revealed only sinus tachycardia until the 24th day of his illness, when ST-T wave changes compatible with myocarditis were noted.

The ECG findings gradually returned to normal over a period of six weeks, after which progressive ambulation was permitted. No cardiovascular sequelae were noted upon his discharge to duty.

An important observation in this epidemic was that a previously healthy, young soldier with influenza A or the influenza-like syndrome could have such a serious complication as myocarditis late in the course of the illness or during convalescence, with a resting tachycardia as the only clinically suggestive sign. Had electrocardiographic studies not been done, this complication would not have been recognized and therefore not treated. Out of a total of 3,400 cases of clinical influenza seen during the epidemic, there were 4 (0.12 per cent) with myocarditis. No specific therapy was given these four patients, except bed rest with bathroom privileges only, until the ECG returned to normal; thereafter, a gradual return to full activity was carried out. No complications developed subsequently, to our knowledge.

Pneumonia

The incidence of pneumonia (all types) with x-ray confirmation in this epidemic was 0.88 per cent. There generally was a marked delay in resolution, despite intensive use of antibiotics. This is well illustrated in cases 2 and 3. In both cases, the pneumonia had not completely cleared even two months after onset. In these two cases the temperature remained normal after the antiobiotics were discontinued, in spite of the continued presence of pneumonic infiltration.

Fever

In uncomplicated cases, the temperature ranged from 101° to 104°F for three to five days, with return to normal by crisis or lysis and an afebrile course thereafter.[1] There was no discernible difference in the effect of Aureomycin and of APC (aspirin, phenacetin, and caffeine) on the duration or degree of fever in these patients.[5] A few cases showed unpredictable swings of temperature, with elevation for one or two days, then a drop to normal for four or five days, and then a sudden elevation and subsidence, only to be repeated some days later. Cases of this type were screened carefully for complications. Occasionally a roentgenogram of the chest revealed a pneumonic infiltration for the first time, following such a flare-up in temperature. The medical staff quickly became aware of the deceptive character of the temperature curve in clinical influenza and remained on the alert for relapses during the patient's convalescent period.

Prostration

There often was profound weakness during the first days of illness, but this generally decreased after two to three days. Many of the soldiers, with the phenomenal recuperative powers of youth, would rebound from a state of hyperpyrexia, extreme lethargy, and weakness on the day of admission to exuberance, high spirits, and impatience at remaining away from their units, in the brief space of three or four days. However, post-influenzal asthenia was present in noteworthy degree in an occasional patient. It was necessary to retain these latter patients in the hospital until the asthenia had completely disappeared, before their return to duty.

Role of Antibiotics

It was our impression that neither antibiotic nor chemotherapeutic agents in any combination had any specific effect in altering the course of these diseases. In some instances, after about ten days of fever despite the use of combinations of antibiotics, a drop in temperature followed the addition of another antibiotic, but this might have been coincidence. It is our belief that the influenza virus has a pathogenicity of its own for which no appropriate medication is available at present, and that the treatment must consist of employing sound medical principles of therapy, good nursing care, supportive measures, and constant vigilance of the patient to recognize complications as they arise.

In case 1, the use of a combination of antibiotics suppressed the normal bacterial flora of the respiratory tract so completely that a pure culture of *M. albicans* was obtained. The patient continued to run a protracted, severe, febrile course, and it is possible that moniliasis may have contributed to his symptomatology in the latter phases of his illness. Several observers have reported that with extensive use of antibiotics and suppression of the normal bacterial flora of the respiratory tract, pulmonary moniliasis may develop.[6] This is one of the hazards of the prolonged use of antibiotics in large doses.

Laboratory Studies

Routine throat and sputum cultures taken during this epidemic revealed a wide variety of organisms, including neisseria, pneumococci, alpha streptococci, and *Hemophilus influenzae*. Because the latter has been noted frequently in epidemics of influenza, we compared its relative prevalence in sputum and throat cultures for the first quarters of 1950 and 1951 respectively. As shown in table 1, only 8.9 per cent of the cultures taken in the first quarter of 1951 were positive for *Hemophilus influenzae,* as compared with 12.9 per cent for the first quarter

of 1950. A random sampling of 10 blood specimens taken for heterophil antibody studies showed a titer of 1/112 in four cases, of 1/224 in four cases, of 1/448 in one case, and of 1/3584 in one case. In all except this last case, which proved to be one of infectious mononucleosis, the titer dropped on absorption with guinea-pig kidney and with boiled beef cells, especially with the guinea-pig kidney absorption test. In the last case, the titer after absorption with guinea-pig kidney was 1/1792 and after absorption with boiled beef cells was negative.

TABLE 1. *Comparison of the prevalence of* Hemophilus influenzae *in throat and sputum cultures, Fort Dix, first quarter of 1950 and first quarter of 1951*

	1950				1951			
	Jan.	Feb.	Mar.	Total	Jan.	Feb.	Mar.	Total
Number of throat cultures	15	7	23	45	137	203	123	463
Number of sputum cultures	14	13	13	40	64	93	35	192
Total	29	20	36	85	201	296	158	655
Number positive for H. influenzae	2	4	5	11	21	31	6	58
Per cent positive for H. influenzae	6.9	20.0	13.9	12.9	10.4	10.5	3.8	8.9

Results of Treatment

No deaths occurred in our series of approximately 3,400 cases of clinical influenza, in contrast to the large number of deaths in older people noted in the 1951 epidemic in the area of Liverpool, England.[7] While the vigor and youth of our group of patients were factors of prime importance in determining the favorable course of this particular epidemic, careful medical observation, good nursing care, and prompt institution of supportive measures, including oxygen and parenteral fluids, played an important role in facilitating the recovery of the seriously ill patients.

SUMMARY

In a series of approximately 3,400 cases of influenza A and an influenza-like syndrome hospitalized during an explosive epidemic of mixed etiology in early 1951 at Ft. Dix, N. J., a few cases assumed an unusually severe and malignant form. Myocarditis, an important though infrequent complication, appeared late in the course of the illness or during convalescence in 0.12 per cent of the cases. Pneumonia with markedly delayed resolution despite intensive use of antibiotics and chemotherapy

occurred in 0.88 per cent. In one of the four cases presented, moniliasis developed as a consequence of antibiotic therapy. Neither antibiotics nor chemotherapeutic agents had any specific effect in altering the clinical course, nor was there any salutary effect from any combination of drugs; however no deaths occurred in this series of 3,400 cases in which the most effective treatment given proved to be nursing and prompt supportive measures.

ACKNOWLEDGMENT: The authors wish to thank Colonel William B. Foster, MC, USAR, Lt. Colonel James L. Hansen, MC, USA, Lt. Colonel Andrew Fodor, MSC, USAR, Lt. Colonel Warren N. Christopher, MSC, USAR, and Major John P. Dwyer, MSC, USAR, for their cooperation and assistance in this study.

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RAPID DETECTION OF ORGANIC BROMIDES IN BIOLOGICAL FLUIDS

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THE UREIDES (*e. g.*, bromisovalum and carbromal), next to the barbitrates, are the most common sedatives found in toxicological specimens submitted to this laboratory. Several methods are available for the estimation of bromides in biological specimens. They depend on the determination of bromides or bromine by iodometric titration,[1] or by color formation with gold chloride[2] or rosaniline.[3] These procedures have useful applications; however, for toxicological identification a more rapid technic was sought for the analysis of bromides in biological fluids, usually in gastric washings, urine, and blood.

This laboratory has adapted Feigl's[4] spot test for inorganic bromine for the identification of organic bromide. The method depends on the formation of red eosin from yellow fluorescein when the latter is exposed to bromine vapor.

The extraction and fusion methods of previously described identification procedures for bromisovalum[5] and carbromal[6] were adapted for use in detecting these organic bromides in biological specimens. Because ureides are classified among "weak acids or non-acids,"[7] the extraction is performed just below neutral pH.

METHOD

To a separatory funnel, introduce 10 to 50 ml of fluid specimen and add to it five times the volume of chloroform. Then add a few drops of 10 per cent HCl to adjust the pH to about 5 to 6, using a pH indicator paper. Shake the funnel for five minutes. Filter the chloroform extract through Celite (Johns-Manville) into a beaker, and evaporate on a hot plate until almost dry.

Collect the residue by dissolving in ethyl ether and transfer it to a 10 by 75 mm Pyrex or other borosilicate glass tube. Dry the ether extract in the tube by gentle heating in a water bath. Mix approximately three times the amount of solid sodium carbon-

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ate thoroughly with the residue and heat the mixture in a hot flame until decomposition is complete. Plunge the bottom of the hot tube into 5 ml of water contained in a small beaker and stir the mixture. Cool the solution and acidify it with an excess amount of glacial acetic acid.

Transfer the entire amount of the solution into a 50-ml Erlenmeyer flask. Add to the solution about 10 mg of lead peroxide powder. Close the mouth of the flask with a sheet of filter paper impregnated with fluorescein (0.1 per cent in alcohol), and bind with a rubber band. Apply freshly dried, impregnated paper.

Prepare a reagent blank and a standard in the same manner. Use a small amount of potassium or sodium bromide as a standard; 20 to 50 μg of bromine is a convenient working range.

Warm the flask gently on a hot plate for about five minutes. Depending on the amount of bromine present, a circular red fleck of varying intensity is formed on the yellow test paper at varying periods of time after the beginning of the heating process.

DISCUSSION

The speed with which the circular red fleck appears, depends on the concentration of bromine. Table 1 shows the rate of the appearance of red eosin color. The minimum amount that can be detected by this method is 10 μg of bromine, provided the fluorescein solution is prepared fresh from time to time. A solution that had been kept on the shelf in this laboratory for six months could detect only a minimum of 30 μg of bromine.

TABLE 1. *Typical rate of appearance of eosin color*

Micrograms of bromine	Time in seconds*
500	15
200	20
100	45
50	60
20	100
10	120

*Measured from the beginning of the heating process.

There is no significant loss of bromide when a bromide-sodium carbonate flux is heated over a high temperature burner (700° to 800° C). This was confirmed by fusing a known amount of bromide (10 to 50 μg of bromine) with sodium carbonate, and measuring the rate with which the converted eosin appeared on the paper in comparison with standard bromine samples that were not fused.

Natural constituents in biological fluids, including normally occurring traces of bromine, do not interfere with this test, nor do some of the compounds that occasionally occur in acid chloroform extracts, such as salicylates, phenobarbital, amobarbital, hexobarbital, acetanilid, and acetophenetidin.

SUMMARY

A rapid and simple procedure is described for the detection of organic bromides in biological fluids. Feigl's technic for the spot test of inorganic bromine has been adapted for organic bromide identification.

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CAN MEDICINE PREVENT WARS?

"Wars obviously have had a large influence on the growth and development of medicine and surgery. Can medicine come to have an influence in thwarting the occurrence of wars? I believe it can and should take steps to wield its influence in helping to bring about a warmer spirit of wanting to understand our fellow man in other areas of this troubled world. No remedy can equal the solvent action of unfeigned sympathy in dispelling the perplexing anxieties, cares, and vexations of life. When will the nations of this earth come to consider themselves as one people whose fortunes rise or fall with any others?"

—OWEN H. WANGENSTEEN, M. D.
in *Journal Lancet*
p. 402, Nov. 1957

THE DETERMINATION OF SERUM CHOLESTEROL

Use of Liebermann-Burchard Reagent in Zak Procedure

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IN 1954, Zak and co-workers[1] described a procedure for serum cholesterol wherein color was developed by adding a concentrated sulfuric acid solution of ferric chloride after the alcohol-acetone filtrate had been evaporated in a conical centrifuge tube and the residue taken up in glacial acetic acid. Although analytically satisfactory in experienced hands, the Zak technic is objectionable on three grounds:

1. Extreme care is necessary in order to avoid accidents in the repetitive pipetting of comparatively large volumes of sulfuric acid.

2. Even minor charring at the acetic acid-color reagent interface as the latter is added will result in errors that are difficult to detect in the presence of the normal deep-purple shading.

3. The color reagent must be either prepared daily (time consuming because ferric chloride dissolves in sulfuric acid with difficulty), or it must be thawed after being stored in the deep freeze. Both alternatives result in delay.

In an effort to avoid such objections, we decided to apply the Liebermann-Burchard reagent to the Zak procedure. This reagent meets all three requirements in that it requires considerably less volume sulfuric acid; is completely compatible with acetic acid, obviating the possibility of mixing errors; and can be freshly prepared daily in a few moments. The complete technic as practiced in this laboratory has been evaluated over the past 18 months.

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PROCEDURES

Equipment

1. Volumetric flasks, 25 ml, glass-stoppered.
2. Pipettes, volumetric transfer, calibrated to deliver 1 ml; Ostwald-Folin, 0.5 ml.
3. Buret, 10 ml, with 0.5 ml graduation.
4. Filter paper, Whatman No. 41, made fat-free by washing with ether and drying.
5. Glass stirring rods, approximately 3 mm outside diameter, and 6 inches long.
6. Cuvettes, for Beckman model B, 1 cm light path, 1.5 ml capacity.
7. Funnels and 50 ml Erlenmeyer flasks.

Reagents

1. *Alcohol-ether mixture,* 3:1. Mix 3 volumes of 95 per cent alcohol (U. S. P.) with 1 volume of anhydrous peroxide-free ether (AR).
2. *Glacial acetic acid* (99.5 per cent U. S. P.). Must be clear and free of extraneous material.
3. *Acetic anhydride-sulfuric acid reagent,* 20:1. Place 20, 40, or 60 ml of cold acetic anhydride in a dry, well-stoppered mixing cylinder and slowly add 1, 2, or 3 ml, respectively, of cold concentrated sulfuric acid. Mix with care by repeated inversion. Cool until the temperature of the reagent is between 23° and 25° C. Use within 1 hour.
   a. Acetic anhydride (ACS).
   b. Sulfuric acid, concentrated (ACS). Must be colorless.

Component parts of the color reagent are stored in a refrigerator to speed cooling of the reagent before use.

4. *Cholesterol standards.*
   a. Stock standard = 1 mg cholesterol/ml. Place 500 mg of freshly recrystallized free cholesterol in a 500-ml volumetric flask; dissolve in glacial acetic acid, by heating, if necessary; cool to room temperature and dilute to volume with same.
   b. Working standards (S_1 - 0.1 mg/ml; S_2 - 0.2 mg/ml; S_3 - 0.4 mg/ml). Into three 50-ml volumetric flasks pipet respectively 5, 10, and 20 ml of stock standard; dilute to volume with glacial acetic acid. Should be prepared fresh every two or three weeks.

Technic

1. Place approximately 15 ml of alcohol-ether mixture into a 25-ml volumetric flask and add 1 ml of serum or plasma from a transfer pipet, drop by drop, while agitating the flask.

2. Heat flask to boiling in a water bath; dilute almost to volume with alcohol-ether mixture; allow flask to come to room temperature.

3. Dilute to volume with alcohol-ether, stopper, and mix by shaking and inversion.

4. Filter through fat-free Whatman No. 41 filter paper into a 50-ml Erlenmeyer flask, draining off last drop by touching lip of volumetric flask to filter paper.

5. Immediately pipet 1-ml aliquots of the filtrate into two conical, 15-ml, centrifuge tubes.

6. Evaporate aliquots to dryness in a hood, using dry air and heat from an infrared heat lamp (fig. 1). Remove from heat as soon as they are completely dry. Samples may be covered and stored at this point.

7. To each tube add 0.5 ml of glacial acetic acid from a buret; place a glass stirring rod in each tube and mix to ensure complete solution.

8. Place 0.5 ml glacial acetic acid into another centrifuge tube for use as a blank; pipet 0.5 ml of each of the three working standards in duplicate into centrifuge tubes; place a stirring rod in each tube.

9. Add 1 ml of freshly prepared and cooled acetic anhydride-sulfuric acid reagent to the blank and first three tubes; mix with the stirring rod, and place tubes in a 25° C, light-tight water bath; add reagent to three tubes every 2 minutes and treat as above. (The order in which the tubes are colored is not important as long as they are read in the same order as colored.)

10. Transfer samples to cuvettes and read % T setting blank at 100% T in a Beckman model B spectrophotometer at 660 millimicrons (red tube) exactly 45 minutes after addition of coloring reagent.

Note: Care must be taken to exclude moisture throughout the procedure.

Calculations

Convert all % T to optical densities

Then (1) $\frac{\text{OD of standard}}{\text{mg of standard}} = K$

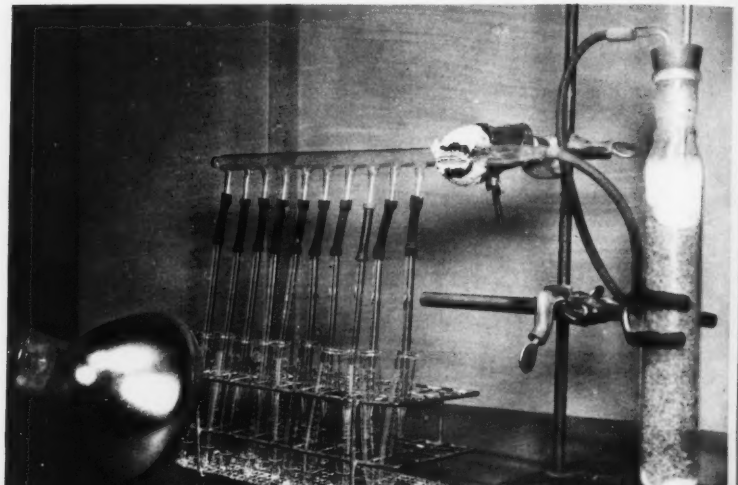

Figure 1. Evaporation. Air is first blown through a container of drying compound (calcium chloride, Silica Gel, or Drierite) to remove all moisture. Air is then directed into the sample tubes by means of a manifold with fine tips. An infrared heat lamp is placed about 6 inches from the sample tubes to speed evaporation.

A K value is obtained from all standards run and an average K value calculated. This value is used in calculating unknown concentrations.

$$(2) \qquad \text{mg\% unk} = \frac{\text{OD unk}}{\text{K}} \times 25 \times 100$$

25 = dilution factor (1 ml serum or plasma in 25 ml)

100 = factor for converting to mg%

Sample Calculations

(1) OD of S_2 = 0.248

mg in S_2 = 0.1 mg

$$\frac{0.248}{0.1} = 2.48 = \text{K}$$

(2) OD of unk = 0.187

$$\text{mg\% unk} = \frac{0.187}{2.48} \times 25 \times 100 = 188 \text{ mg\%}$$

If the concentration is above 350 mg%, use only 0.5 ml serum or plasma (so that % T will be within those of the standards) and double the value obtained in equation No. 2.

DISCUSSION

In those instances where a total cholesterol analysis is required, and no need for an estimation of cholesterol ester concentration exists, the primary requisites of any procedure are time and convenience. The disadvantages of the ferric chloride technic described by Zak and associates have already been enumerated. In the standard Bloor[2] technic the step involving evaporation to dryness in a beaker requires continued attention and care. We believe, therefore, that the procedure outlined above combines the best features of those described from the standpoint of time, convenience, and adaptability to relatively inexperienced personnel. In the course of a year and a half, at this facility, approximately 1,200 human serum samples were run on a routine basis for total cholesterol concentrations. Of these, 177 were repeated on different days and 92 were analyzed twice on the same run (duplicates). In many instances a run consisted of up to 60 samples. As indicated in table 1, the number of repeats that checked on different days within 10 per cent was 92 per cent; the number of duplicates that checked within 10 per cent was 97 per cent.

As a check on the accuracy of this method, many recovery and comparison studies were run. Recoveries of 95-100 per cent were recorded when varying amounts of cholesterol were added to serum. Comparisons with the Bloor technic have shown agreement within 10 per cent for a range of approximately 50-800 mg per 100 ml.

TABLE 1. *Variation in results on duplicate and repeat samples*

	Duplicate samples (analyzed twice on the same run)			Repeat samples (analyzed on two different days)		
	Number	Per cent variation* less than	Per cent of total	Number	Per cent variation* less than	Per cent of total
	66	3	72	126	5	71
	23	3-5	25	37	6-10	21
	3	6-15	3	14	11-20	8
Total	92		100	177		100

*Per cent variation was determined by dividing the difference between the values obtained for a sample by the average of those values.

SUMMARY

A procedure for the determination of total serum cholesterol combining the best features of those described to date in the literature, and eliminating many of the difficulties that hinder successful routine adaptation has been recorded. The convenience of this technic has been extensively evaluated over an 18-month period on approximately 1,200 serum samples.

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THE GREATNESS OF HIPPOCRATES

"It must have been a marvelous experience to have sat under the branches of the old plane tree on the Isle of Cos, listening to Hippocrates as he demonstrated his patients, and following the working of a master mind. Today, it may not seem remarkable that Hippocrates, in making a diagnosis, took the patient's history, inquired carefully about his present illness, his past history, his family history, his habits, his work, where he lived, what he ate and drank, and then made a careful physical examination, employing inspection, palpation, and auscultation, following this with a careful examination of sputum, urine, and stools. But in Hippocrates' day, soothsayers, astrologers, and the priests of various cults often dominated medical practice. They made their diagnoses by studying the stars, by examining the organs of sacrificial animals, by interpreting dreams, by studying omens and portents. This makes the achievement of Hippocrates stand out in bold and dramatic relief."

—RALPH H. MAJOR, M. D.
in *International Record of Medicine*
p. 485, Sept. 1957

FORMATION OF MYELIN FORMS IN BRAIN TISSUE

Effect of Surface-Active Substances

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MYELIN FORMS are peculiar anisotropic, elongated or spherical structures that "grow" on exposure of phosphatides, cerebrosides, and certain other lipids to water. The best known of the myelin forms are those derived from lecithin, which are readily demonstrated by exposing the dried acetone precipitate of an ether extract of brain tissue to water. They have been described by Rinne[1] as liquid crystals (paracrystals) in the mesomorphic state of matter, whereas according to Frey-Wyssling[2] they are not true liquid crystals but a hydration phenomenon associated with the surface-active and heteropolar characteristic of lecithin.

The purpose of this article is to report the development of myelin forms in unfixed whole brain tissue by means of surface-active substances and to explore the possibility that such substances are operative in demyelinating diseases of the brain. In addition to myelin forms, cholesterol crystals and tyrosine crystals developed in some surfactant-brain tissue emulsions indicating breakdown of cerebral lipoproteins. Dioctyl sodium sulfosuccinate (Aerosol OT*), a synthetic detergent, had a controlling influence on the "growth" of myelin forms, probably by orientation of molecular structure. Spiraled myelin forms developed in some surfactant-brain emulsions. Another finding was excitation of myelin forms by toluidine blue and methylene blue. Most of the surface-active substances used in these experiments are synthetic detergents that have a hydrophilic group at one end of the molecule and a lipophilic group at the other.

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Some aspects of this study were discussed at the Symposium on "Allergic" Encephalomyelitis held at the National Institutes of Health, Bethesda, Md., on 19-20 Oct. 1957.[3]

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EXPERIMENTS

Formation of Myelin Forms From Brain Tissue by Means of Aerosol OT

Aerosol OT is practically pure wax-like material, somewhat plastic, with the following chemical structure:

$$C_8H_{17}OOCCH_2$$
$$C_8H_{17}OOCCH$$
$$SO_3NA$$

Its properties are as follows: molecular weight, 444; solubility, 1.5 grams per 100 ml of water at 25°C; forms transparent gels at higher concentrations by the "soaking out" method; soluble in most organic solvents; pH about 6.5 in 1 per cent solution; anionic and somewhat hygroscopic; surface tension in 1.0 per cent solution in water 26 dynes and in 0.1 per cent solution 28.7 dynes.[4]

Guinea Pig Brain Tissue. Ten guinea pigs were killed by intracardiac injection of Pentothal Sodium (brand of thiopental sodium) and the brains removed. The cerebellums were discarded and the cerebrums divided into approximately equal halves by sagittal section through the corpus callosum. One half of each of the 10 brains constituted the experimental group and the other 10 halves the control group.

The brain halves in the experimental group were weighed, placed separately on plate glass, and emulsified with sufficient Aerosol OT to produce a concentration of Aerosol OT in each brain emulsion of 10.6 per cent. A small portion was placed on a slide and covered with a coverglass. Pressure was applied to the coverglass to obtain a thin spread, before sealing with clear varnish.

The control group of brain halves was emulsified without adding any of the surface-active agent, and slide preparations similar to those of the experimental group were made.

Daily observations were made of both experimental and control preparations with bright field and polarizing microscopes with particular attention to the formation of myelin forms and cholesterol crystals. All preparations were at a room temperature of 23°C.

Results. Myelin forms developed within 24 hours and persisted in all of the experimental preparations. In contrast, all of the control preparations were negative for myelin forms until the 20th day, when three of them became positive.

When the emulsions were first placed on a slide there was only a finely granular, translucent substance visible under a microscope. Within 24 hours, large oval or round spaces containing myelin forms appeared in the emulsion. Under the bright

field microscope the myelin forms were round, oval, or elongated structures with highly refractile, thick or thin walls, which formed intricately tangled masses (figs. 1 and 2). Under the polarizing microscope the myelin forms were anisotropic, the most brilliant anisotropy occurring in the walls; when the myelin forms were spherical or when the tip of a developing myelin form was oriented in a certain way they appeared as Maltese crosses (figs. 3 and 4).

Within some of the spaces in the emulsion, together with the myelin forms, there was Aerosol OT, which was opalescent, homogeneous or striated, and less refractile than the myelin forms on bright field observation (figs. 1 and 2). Under the polarizing microscope, Aerosol OT appeared as anisotropic, interlocking fan-shaped plates, which were either homogeneous or longitudinally striated; the anisotropy was less than that of the myelin forms (figs. 3 and 4). Cross striations in the myelin forms appeared on the 25th day. On the 28th day of the experiment, elongated myelin forms that were oriented perpendicularly to the striations of Aerosol OT appeared, indicating that the molecular arrangement of the surface-active agent exerted a controlling influence on the molecular arrangement of the myelin forms.

It is to be emphasized that the myelin forms show dynamic "growth," imperceptible to the eye over a period of days. In some preparations, after a period of two weeks, the myelin forms underwent degenerative changes indicated by loss of anisotropism and shape. Myelin forms, although developing preferentially in foci containing Aerosol OT, also developed in the emulsion and at its periphery.

The optical sign of the myelin forms and the spherules was positive, as determined with the Red I retardation plate and the polarizing microscope. The positive optical sign indicates that the molecules in the myelin forms are oriented with their optic axes radially, as is the myelin in peripheral nerves.

In the experimental preparations cholesterol crystals formed within 24 hours in 8 of 10 emulsions, whereas in control preparations a crystal was present in only one emulsion after 20 days. Cholesterol crystals appeared as early as 30 minutes after the brain was mixed with Aerosol OT. The crystals were flat, somewhat rectangular, anisotropic, and under the polarizing microscope appeared to be brilliantly multicolored (figs. 5 and 6). On standing, the crystals increased in size.

Tyrosine crystals were noted in 4 of the Aerosol OT-brain emulsions on the 18th day.

In the control preparations there were numerous small anisotropic structures. A few myelin forms were noted in three control preparations on the 20th day. Only a few were well formed (figs.

Figure 1. The myelin forms are the smaller refractile curved bodies in a lake of hemogeneous Aerosol OT. Aerosol OT-guinea pig brain emulsion. Seventh day of experiment. (× 305)

Figure 2. Detail of figure 1. (× 630)

Figure 3. Same area as figure 1, photographed under the polarizing microscope. The smaller bodies that exhibit Maltese crosses are myelin forms. Aerosol OT is represented by diffusely anisotropic fan-shaped areas in the background. (× 305)

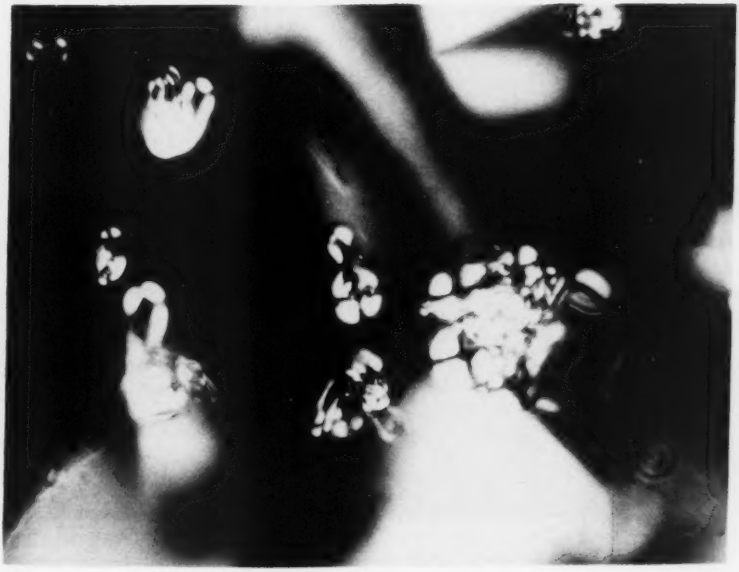

Figure 4. Same area as figure 2, photographed under the polarizing microscope. (× 630)

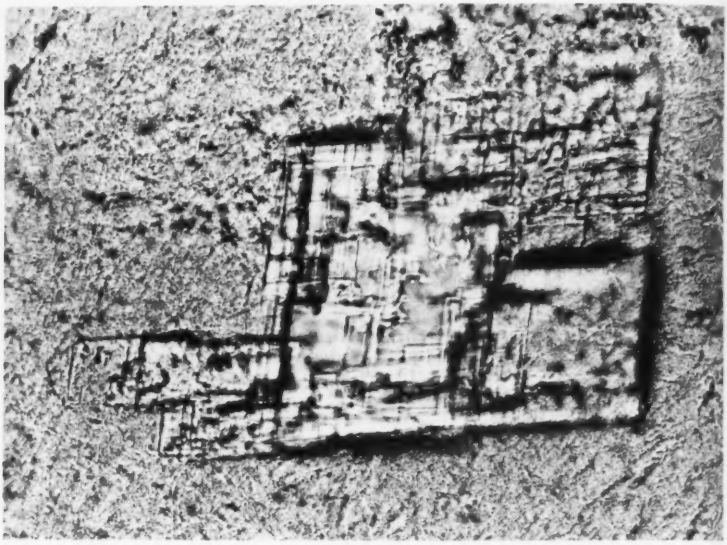

Figure 5. Cholesterol crystal in Aerosol OT-guinea pig brain emulsion. Seventh day of experiment. (× 305)

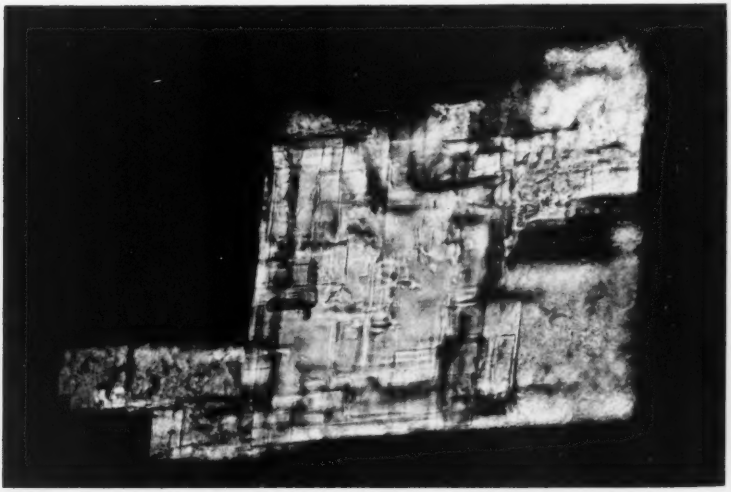

Figure 6. Same crystal as in figure 5, photographed under the polarizing microscope. (× 305)

7 and 8). The myelin forms had the same appearance as those in the experimental preparations, and formed in large spaces and at the periphery of the emulsions. No tyrosine crystals were noted. A few cholesterol crystals were present in one preparation.

Human Brain Tissue. A fresh brain was obtained at autopsy of a white man, 24 years of age, who died from a subdural hematoma. Five grams of white matter from the corpus callosum was emulsified on a glass plate with a spatula. Aerosol OT was thoroughly mixed with brain tissue in the quantities shown in table 1.

TABLE 1. *Amounts of Aerosol OT added to human brain tissue*

Emulsion number	Amount of Aerosol OT	
	mg	%
1 (Control)	None	0.0
2	100	2.0
3	200	3.9
4	500	9.0
5	1000	17.0

A portion of each emulsion was placed on a slide, covered with a coverglass and sealed as described previously. Additional preparations were made to study the effect of adding water to an Aerosol OT-brain emulsion. Emulsion 5, which contained 17 per cent Aerosol OT, was diluted successively with 0.5, 1, and 2 ml of distilled water. Slide preparations were made from each dilution as previously described, and were designated as emulsions 6, 7, and 8, respectively.

Results. Myelin forms developed in emulsions containing 2, 3.9, and 9.0 per cent Aerosol OT within 24 hours, but did not develop in emulsion 5 which contained 17 per cent Aerosol OT, or this emulsion diluted with 0.5 ml of distilled water. On further dilution of emulsion 5 with 1 ml and 2 ml, however, sparse and poorly formed myelin forms developed on the fifth and fourth day, respectively.

The myelin forms were similar to those in the Aerosol OT-guinea pig brain emulsion, but were more plentiful (fig. 9). After the 5th day, and particularly in emulsions 3 and 4, the myelin forms exhibited numerous fine cross striations, were subjectively multicolored under the polarizing microscope, and completely filled or traversed spaces in the emulsion as sweeping gracefully curved structures (figs. 10, 11, and 12); striated myelin forms of this type were found in Aerosol OT-guinea pig brain emulsions only after the 25th day.

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Figure 7. Myelin forms in control guinea-pig brain emulsion. The presence of such well developed myelin forms in a control preparation was most unusual. (× 305)

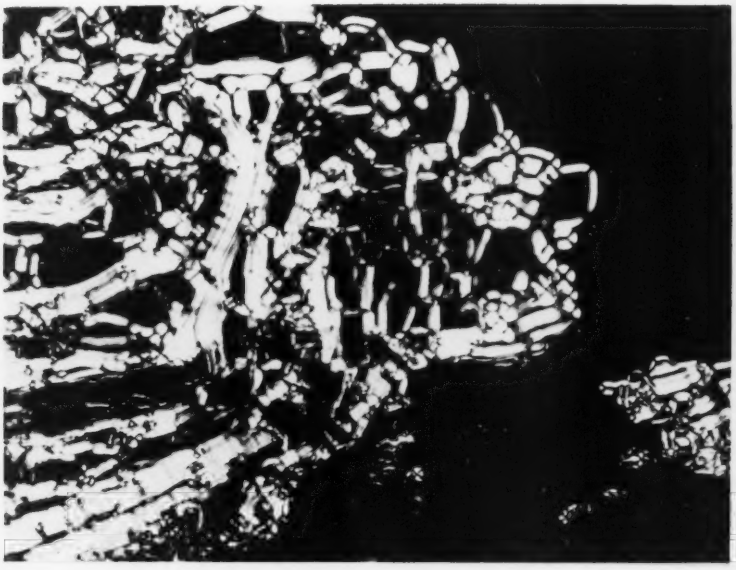

Figure 8. Same area as figure 7, photographed under the polarizing microscope. Twenty-fifth day of experiment. (× 305)

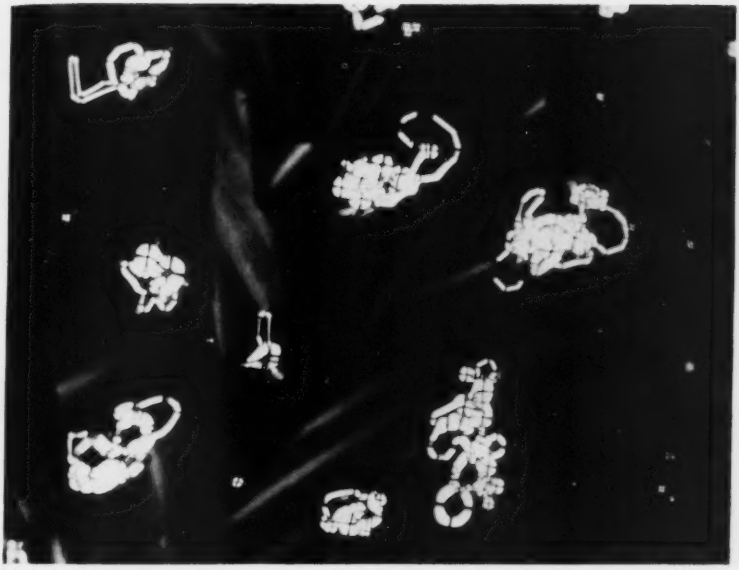

Figure 9. Myelin forms in Aerosol OT-human brain emulsion No. 4. Note the difference in brilliance of the anisotropy of the myelin forms as compared to the background Aerosol OT. Fourteenth day of experiment. (× 305)

Figure 10. Myelin forms exhibiting fine cross striations in Aerosol OT-human brain emulsion. In the upper portion of the illustration is a straight edge of a cholesterol crystal. Fourteenth day of experiment. (× 305)

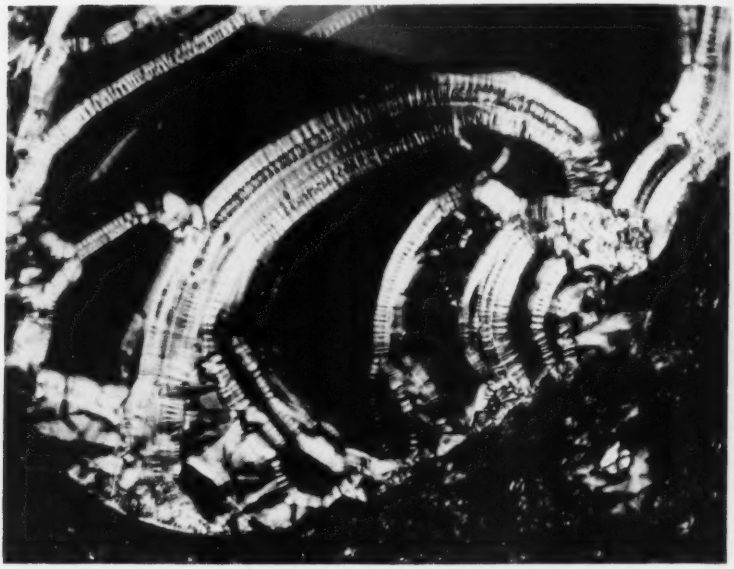

Figure 11. Same areas as figure 10, photographed under the polarizing microscope. (× 305)

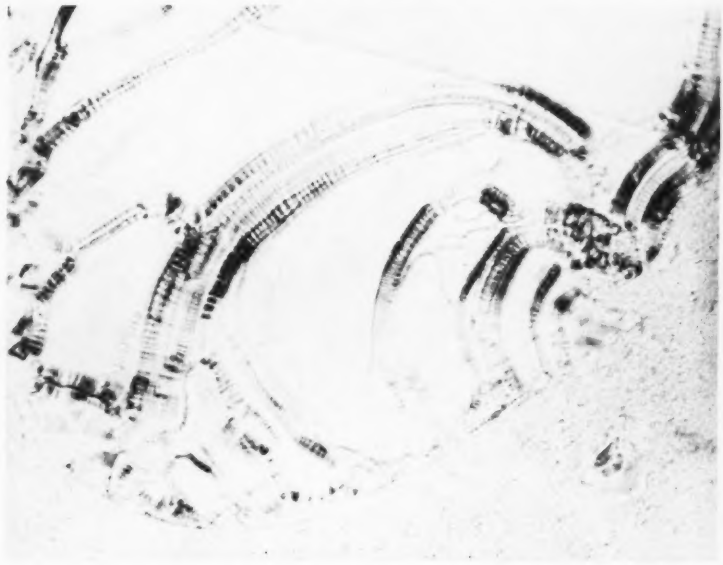

Figure 12. Same area as figures 10 and 11 but photographed with uncrossed nicols and a red filter to accentuate cross striations in myelin forms. (× 305)

Thread-shaped myelin forms developed earlier than in the Aerosol OT-guinea pig brain emulsions and likewise "grew" at right angles to the longitudinal striation of Aerosol OT as observed between crossed nicol prisms (figs. 13, 14, and 15). When there was an abrupt change in the direction of the striation in the surfactant, myelin forms likewise changed direction, indicating control of the molecular arrangement of myelin forms by the molecular structure of Aerosol OT. Myelin forms derived from human brain tissue were optically positive. Aerosol OT was optically positive in the direction of its longitudinal striations, but examination of spherules of Aerosol OT indicated that in relation to the optic axes of their molecules they were optically negative.

Myelin forms traversing Aerosol OT at right angles to the striations of Aerosol OT often had a color complementary to that of Aerosol OT with the Red I retardation plate in place between crossed nicol prisms; that is to say, when Aerosol OT was blue, the myelin forms were yellow, with a reversal of these complementary colors on 90-degree rotation of the preparations. With the same microscopic technic the myelin forms traversing Aerosol OT in older preparations were yellow, regardless of rotation of the stage. These observations suggest that Aerosol OT has the ability to determine the direction of "growth" of myelin forms and possibly to orient their molecular structure from a radial to a tangential pattern in relation to the long axis of the myelin forms.

The spherules or developing tip of a myelin form exhibited a cross of polarization indicated by a dark Maltese cross against four bright quadrants. With the Red I retardation plate between crossed nicol prisms, quadrants 1 and 3 (upper right and lower left) were blue, while quadrants 2 and 4 (upper left and lower right) were yellow. This indicated that the sign of the polarization cross was positive and that the long chains of the component molecules were oriented radially as in most fluid crystalline spherules.[5] Older spherules were laminated and multicolored with the Red I retardation plate in place (fig. 16).

Aerosol OT in certain concentrations is anisotropic and must be differentiated from myelin forms. It is soluble in water, 1.5 grams per 100 ml, and at this concentration was transparent in the bright field and not anisotropic. At concentrations in water above 1.5 grams per 100 ml it was anisotropic, but could readily be differentiated on bright field observation because it was almost transparent and striated longitudinally, whereas myelin forms were highly refractile and had the characteristic shape previously described. Aerosol OT that accumulated in spaces in the brain emulsion appeared between crossed nicol prisms as diffuse or longitudinally striated fan-shaped plates, which at their points of contact exhibited black or white linear areas.

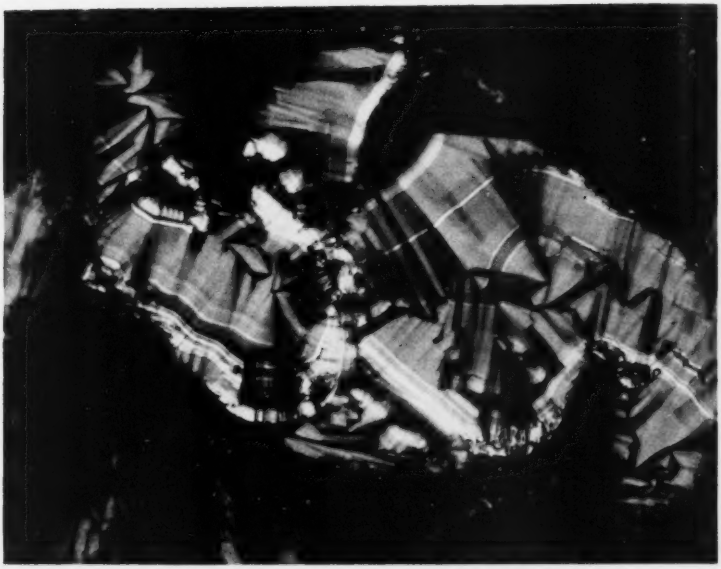

Figure 13. Myelin forms indicated by the fine bright lines are arranged perpendicular to longitudinal striations of Aerosol OT, which demonstrates control of "growth" of myelin forms by Aerosol OT. Photographed under the polarizing microscope with Red I retardation plate in place. Thirty-sixth day of experiment. Aerosol OT-human brain emulsion. (× 365)

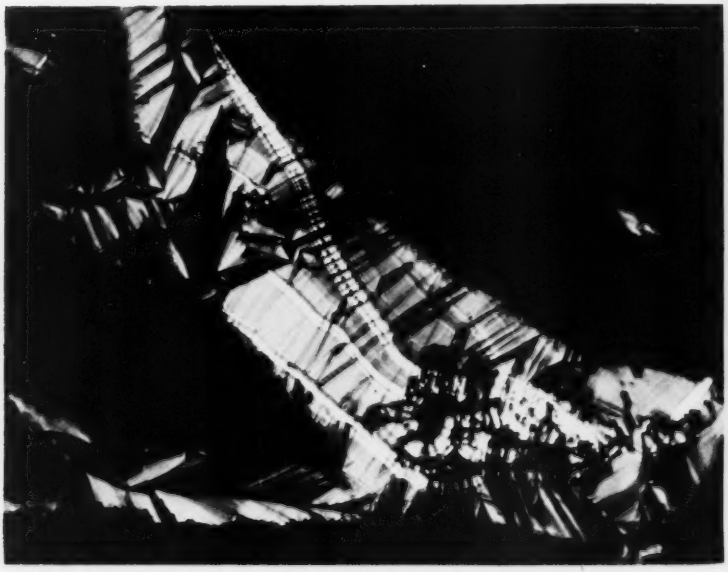

Figure 14. Similar to figure 13 but 80th day of experiment. The myelin forms, indicated by linear bright lines, are more prominent. Aerosol OT-human brain emulsion. (× 305)

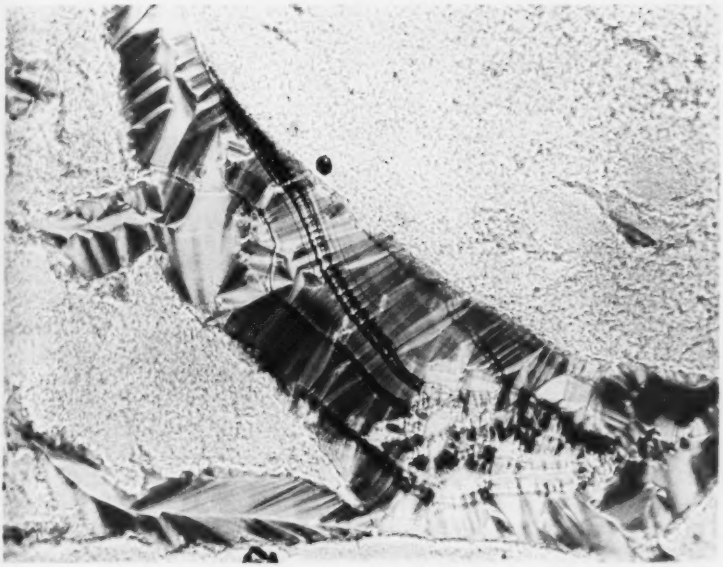

Figure 15. Same area as figure 14 but photographed with green filter to accentuate the yellow lines of myelin forms. (× 305)

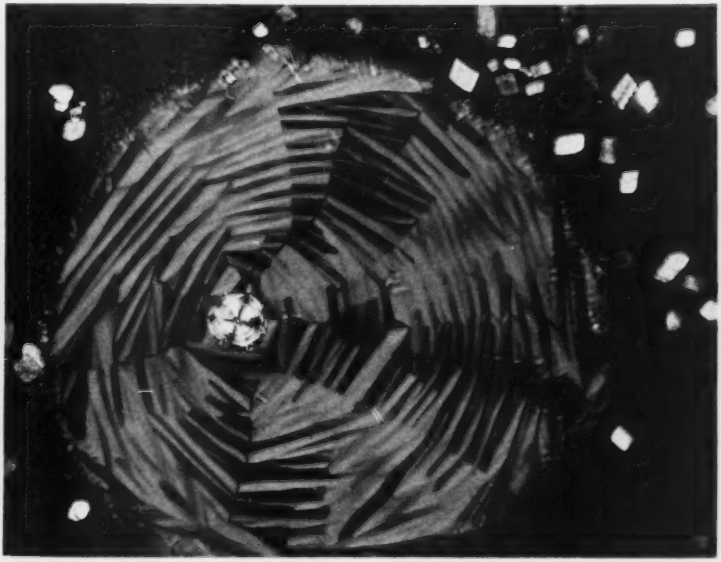

Figure 16. Myelin spherule in Aerosol OT-human brain-water emulsion No. 7. The laminated spherule is located in a lake of Aerosol OT and shows an imperfect Maltese cross. The surrounding brain emulsion contains anisotropic, rectangular cholesterol crystals. Thirty-sixth day of experiment. (× 305)

On dilution of Aerosol OT-human brain emulsion with distilled water, the difference in intensity of anisotropy of myelin forms compared with Aerosol OT was striking.

Spiraled myelin forms were found in dioctyl sodium sulfosuccinate-human brain emulsion on the 80th day after preparation (figs. 17, 18, and 19).

Cholesterol crystals developed within 4 hours in emulsions 5, 6, 7, and 8, and in these latter within 30 minutes; emulsion 5 contained 17 per cent Aerosol OT, and emulsions 6, 7, and 8 were dilutions of this concentrated emulsion with distilled water. No cholesterol crystals formed in control preparations of brain emulsion in 30 days or in emulsion 2, which contained 2 per cent Aerosol OT. Emulsions 3 and 4, which contained 3.9 and 9 per cent Aerosol OT, respectively, showed cholesterol crystals within 24 hours (table 2). The cholesterol crystals were brilliantly multicolored between crossed nicol prisms and were similar to but more numerous than those in Aerosol OT-guinea pig brain emulsions. They were particularly numerous in concentrated Aerosol OT-human brain emulsions diluted with water.

TABLE 2. *Formation of cholesterol crystals in surfactant-human brain emulsions*

Emulsion number	Concentration of Aerosol OT	Days						
		4 hrs.	1	2	3	4	5	10
1	None (control)	-	-	-	-	-	-	-
2	2.0%	-	-	-	-	-	-	-
3	3.9%	-	+	+	+	+	+	+
4	9.0%	-	++	++	++	++	++	++
5	17.0%	+	+++	+++	+++	+++	+++	+++
6	Emulsion 5 with 0.5 ml water	+++	+++	+++	+++	+++	+++	+++
7	Emulsion 5 with 1.5 ml water	+++	++++	++++	++++	++++	++++	++++
8	Emulsion 5 with 3.5 ml water	+++	++++	++++	++++	++++	++++	++++

\+ Indicates 10 to 20 crystals in one preparation.
++ Indicates 20 to 100 crystals in one preparation.
+++ Indicates hundreds of crystals in one preparation.
++++ Indicates thousands of crystals in one preparation.

With increasing dilution of emulsion 5 with water, the crystals began to lose their form, the corners became rounded, and coloration between nicol prisms was decreased.

Formation of Myelin Forms by Means of Various Surface Active Substances

The purpose of this experiment was to establish whether surface-active substances other than Aerosol OT would form myelin forms from whole-brain tissue. Their chemical structure was different, but all had in common the ability to lower the surface tension of water.

Fresh dog brain was emulsified with the surfactants in the proportion of 4.5 grams of dog brain to 0.5 gram of surfactant

Figure 17. Spiraled myelin form in Aerosol OT-human brain emulsion. Eightieth day of experiment. Bright field. (× 305)

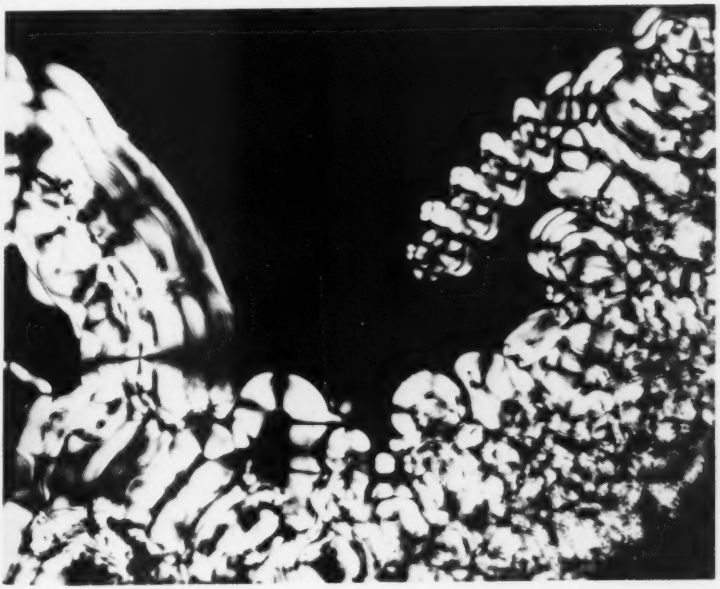

Figure 18. Same as figure 17, photographed between crossed nicol prisms. (× 305)

to make a concentration of 10 per cent, with the exception of cobra venom, which was emulsified in brain in the proportion of 2 mg to 200 mg of brain for a concentration of 1 per cent. A portion of each emulsion was placed on a slide and preparations made as described previously.

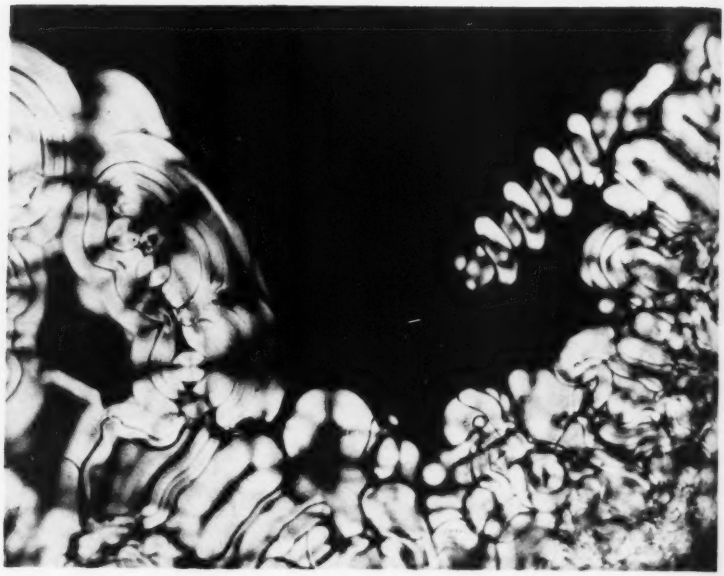

Figure 19. Same as figures 17 and 18 but photographed between crossed nicol prisms with the Red I retardation plate in place. In the original color photograph the background is purple and the myelin forms exhibit gradations of yellow and blue. (× 305)

Results. The results are shown in table 3. It will be noted that myelin forms developed in all of the preparations. Emcol 607,* a cationic quaternary ammonium base, was particularly effective in causing the formation of large, numerous, well developed myelin forms; cobra venom was almost as effective (figs. 20 and 21). Although myelin forms developed in control preparations, they were sparse and not well developed. Spiraled myelin forms were noted in the Santomerse** (salt of a substituted aromatic sulfonic acid) preparation (fig. 22). Cholesterol crystals were noted in the Aerosol OT, Aerosol MA, and Aerosol AY preparations. In the nonionic Igepal Compound*** (an alkyl-aryl-polyglycol) preparation, tyrosine crystals formed. It was

*The Emulsol Chemical Corp., Chicago, Ill.

**Monsanto Chemical Co., St. Louis, Mo.

***General Dyestuff Co., Division of General Aniline and Film Corp., New York, N. Y.

demonstrated that surfactants, other than Aerosol OT, caused the formation of myelin forms and that Emcol 607 was more effective.

TABLE 3. *Formation of myelin forms with various surface-active substances*

Commercial name	Chemical character	Day						Remarks
		1	2	3	4	7	24	
Emcol 607	A quaternary ammonium base (cationic)	+	+	+	+	+	+	
Emcol PL-50-3	Propylene glycol monolaurate	-	-	-	-	+	+	
Santomerse 1	Salt of substituted aromatic sulfonic acid	-	-	-	-	+	+	Spiraled myelin forms
Aerosol OT	Dioctyl sodium sulfosuccinate (anionic)	-	-	-	-	+	+	Cholesterol crystals
Aerosol MA	Dihexyl sodium sulfosuccinate (anionic)	-	-	-	-	+	+	Cholesterol crystals
Aerosol AY	Diamyl sodium sulfosuccinate	-	-	-	-	+	+	Cholesterol crystals
Igepal Compound (high concentration)	An alkyl-aryl-polyglycol (nonionic)	+	+	+	+	+	+	Tyrosine crystals
Cobra venom	Same	+	+	+	+	+	+	Rhomboid crystals

Experiments with Animal Lecithin, Vegetable Lecithin, and Lecithin Extracted from Dog Brain

Dog brain was extracted with ether in the cold, and crude lecithin was precipitated from the ether extract by acetone. The precipitate was dried in vacuo and stored at 1°C.

The crude vegetable and animal lecithins were obtained from a commercial source. A small portion of each lecithin was placed

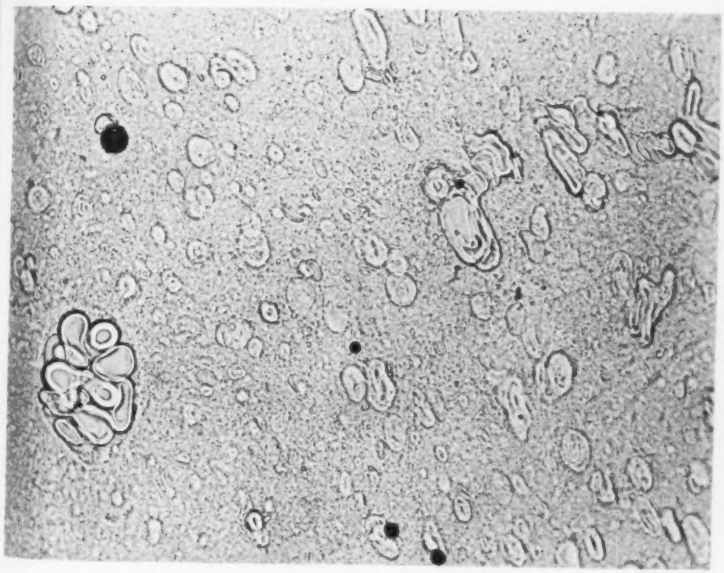

Figure 20. Myelin forms in cobra venom-dog brain emulsion. Bright field. (× 305)

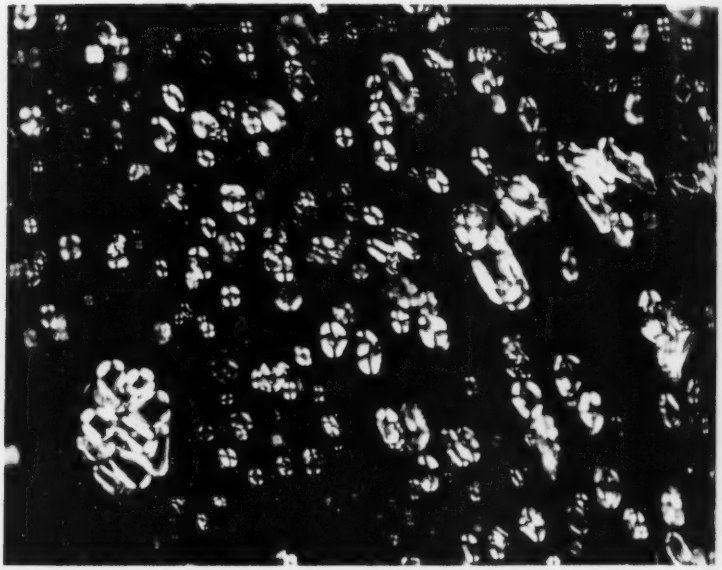

Figure 21. Same as figure 20, photographed between crossed nicol prisms. (× 305)

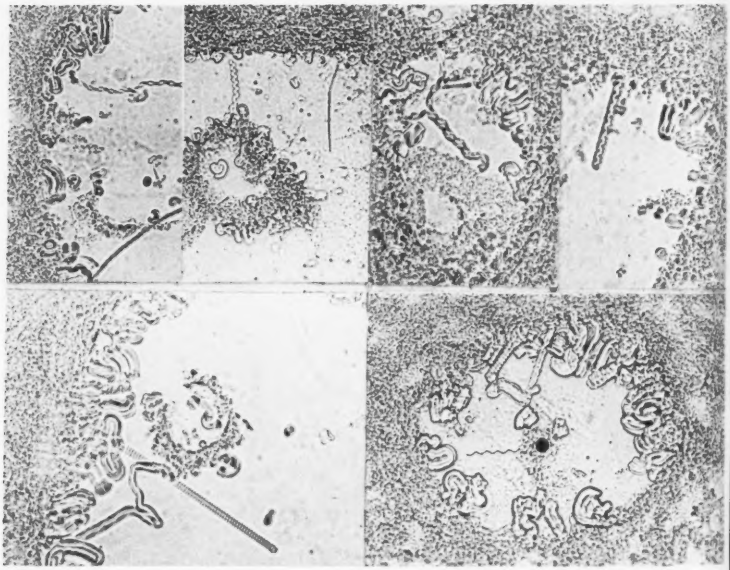

Figure 22. Helical myelin forms resembling spirochetes in Santomerse-dog brain preparation. (× 265)

on a slide, covered with a coverglass and distilled water placed under the coverglass. Within a few seconds, myelin forms, basically similar to those derived from brain tissue, began to "grow" from the edge of the lecithin. The "growth" of the myelin forms was rapid and movement could easily be detected, whereas the movement of myelin forms derived from brain tissue with surfactants could only be captured by means of time-lapse photography. The myelin forms of lecithin like those derived from whole-brain tissue, were anisotropic and optically positive in the direction of the optic axes, and optically negative in the direction of the long axis of the myelin form. Anisotropy of these myelin forms was less than that of the myelin forms derived from brain tissue.

When a portion of Aerosol OT in 25 per cent gel state in water was placed on a slide and covered with a coverglass, and water was placed beneath the coverglass, forms similar to myelin forms "grew" into the surrounding water. When these myelin-form-like structures reached the edge of the coverglass, there immediately was a rapid formation of helical liquid crystals. When Aerosol OT 50 per cent in water-gel state was emulsified with animal lecithin in equal quantities by weight and a similar preparation made, only one type of myelin form "grew" into the surrounding water, indicating the formation of mixed lecithin Aerosol OT liquid crystals. The inference is that Aerosol OT in a mixed liquid crystal with lecithin imparts the ability to form helical structures.

Staining Reactions of Myelin Forms of Lecithins. Myelin forms of lecithin were prepared as described and various stains were permitted to diffuse under the coverglass. (1) Osmic acid (1 per cent aqueous solution); the myelin forms stained brown. (2) Sudan IV (60 per cent propylene glycol); the myelin forms stained yellow and extracted the dye from the solution. Peculiar angular myelin forms developed. (3) Toluidine blue (1 per cent aqueous solution); on exposure to the dye, the myelin forms became very active, divided, and broke down into intensely blue-staining foamy structures. When the myelin forms took up the stain, "growth" was stopped or retarded, and anisotropy reduced or abolished.

Surface Tension Determination on Lecithin

A crude lecithin was extracted from dog brain by a method described by Hawk, Oser, and Summerson.[6] Lecithin was dissolved in distilled water and the surface tension of various concentrations obtained with a du Noüy tensiometer. The results are shown in figure 23. Lecithin reduced the surface tension of water to 37.3 dynes/cm in a concentration of 1 per cent and was still surface active in concentration of 0.000001 per cent (1 to 10,000,000).

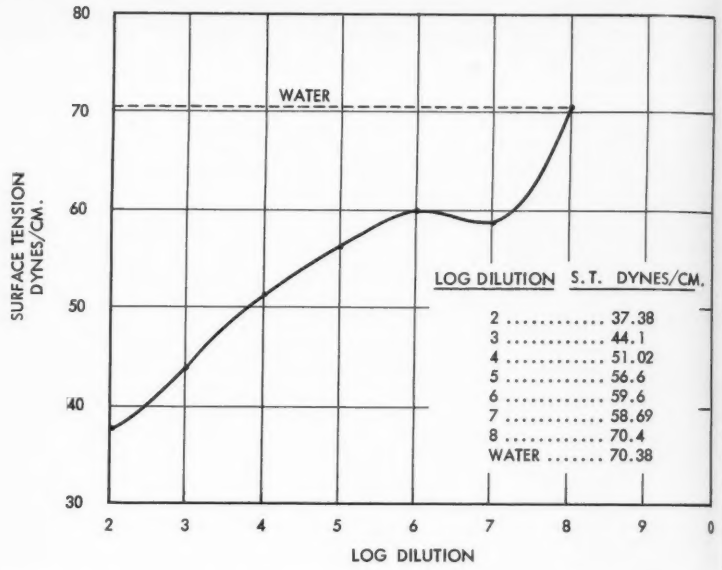

Figure 23. Surface tension of solutions of dog brain-lecithin in water (acetone precipitate of ether extract of wet dog brain).

Demonstration of Myelin Forms in the Acute Lesions of Multiple Sclerosis

Formalin-fixed cerebral tissue was obtained from a 50-year-old white man with long-standing multiple sclerosis who had an exacerbation of neurologic symptoms during an attack of viral hepatitis from which he died. On examination of the brain both acute and chronic lesions of multiple sclerosis were seen. Examination of frozen sections of the brain by polarizing microscopy revealed in demyelinated areas anisotropic spherulitic myelin which had the same optical properties as myelin forms produced by surfactant on brain tissue in vitro (figs. 24, 25, and 26).

Time-Lapse Cinephotomicrography of Myelin Forms

The development of myelin forms from brain tissue by means of surface-active substances, and the development of myelin forms from vegetable lecithin, animal lecithin, crude dog lecithin in the presence of water and surfactants was recorded by means of time-lapse cinephotomicrography. Exposures were taken at 20-second, 1-minute or 5-minute intervals. The mechanism of the development of myelin forms could be accurately determined. Some of the myelin forms "grew" slowly by means of coalescence of minute anisotropic bodies, while others "grew" comparatively rapidly by the hydration phenomenon previously described. One

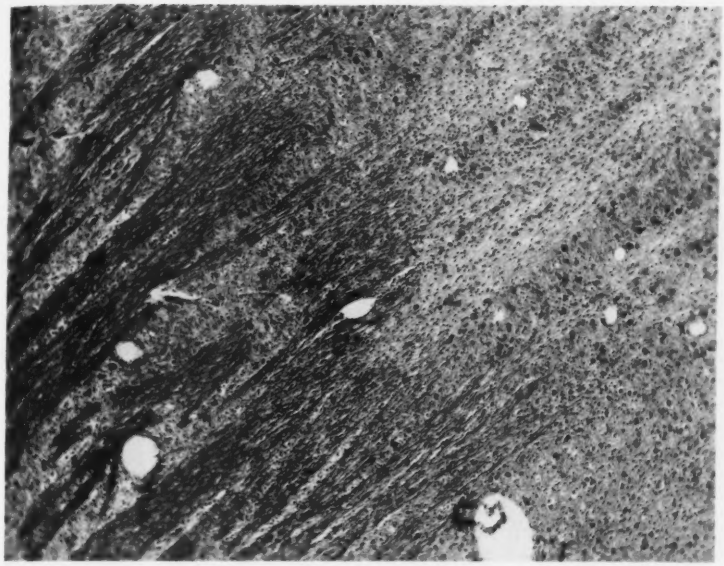

Figure 24. Acute lesion of multiple sclerosis. There is severe demyelination, abrupt termination of myelinated tracts, intact neurones, and infiltration with lipid-laden macrophages. Frozen section. (Hematoxylin-eosin stain, × 50)

Figure 25. Similar to figure 24, but photographed between crossed nicol prisms. Anisotropic myelinated tracts end abruptly at the area of demyelination. In the transition area are spherulitic myelin forms. (× 50)

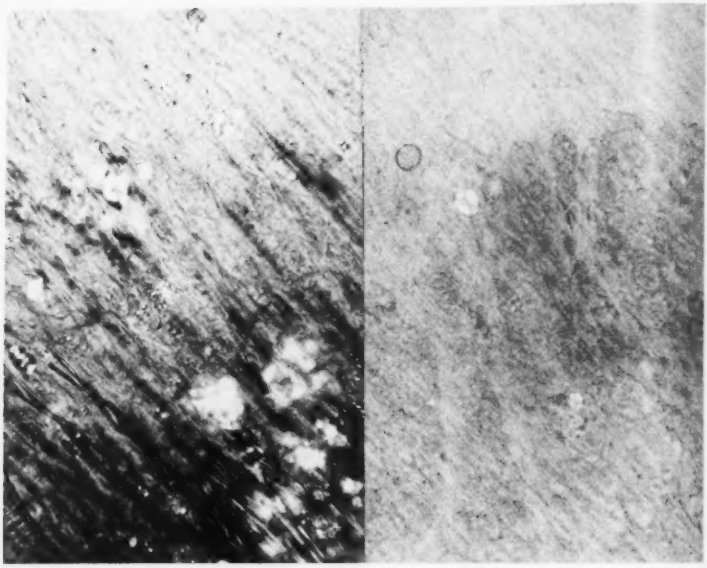

Figure 26. Detail of figure 25. Left: Spherulitic myelin form showing Maltese cross of polarization, photographed between crossed nicol prisms. Right: Same as on the left but photographed with Red I retardation plate in place. The quadrants of the Maltese cross in the original photograph are alternating yellow and blue. The optical sign is positive. (× 525)

myelin form suddenly disappeared, which suggests the possibility of the formation of an explosive gel of brain tissue by means of surfactants. In this regard, Everett[7] discussed the preparation of biological gels with sufficient internal pressure to cause them to explode violently.

DISCUSSION

The experiments demonstrate that the addition of a surface active synthetic agent, dioctyl sodium sulfosuccinate (Aerosol OT), to unfixed whole human or guinea pig brain tissue causes the formation of myelin forms, cholesterol crystals and tyrosine crystals. The mechansim of development of myelin forms is believed to be as follows: The surface-active agent splits cerebral lipoprotein complexes to liberate lecithin. In the presence of water lecithin develops into myelin forms. The choline-phosphoric acid portion of a lecithin molecule is highly water soluble whereas the fatty-acid portion is insoluble in water but soluble in fats. In this regard they are similar to synthetic surface-active agents which also have a hydrophilic and hydrophobic portion to their molecule. Hawk, Oser, and Summerson make the following statement: "If a portion of solid lecithin is placed in water and then observed under the microscope, the lecithin will be seen

to diffuse out into the water in the form of long curving strands ('myelin forms') which bear a remarkable resemblance to the protoplasmic protuberances of lower forms of life."[6]

The mechanism by which the lecithin streams out into water is the attraction of the hydrophilic portion of the molecule to water, while the hydrophobic groups are drawn away from the surface. The molecular orientation in the case of lecithin is shown in figure 27. Myelin forms are usually designated as liquid crystals. However, as Frey-Wyssling pointed out, in a liquid crystalline state one deals with a special aggregate of a uniform substance containing only one component, whereas at least two components take part in the formation of myelin forms, one of which is water. Aerosol OT may be another component of the myelin forms.

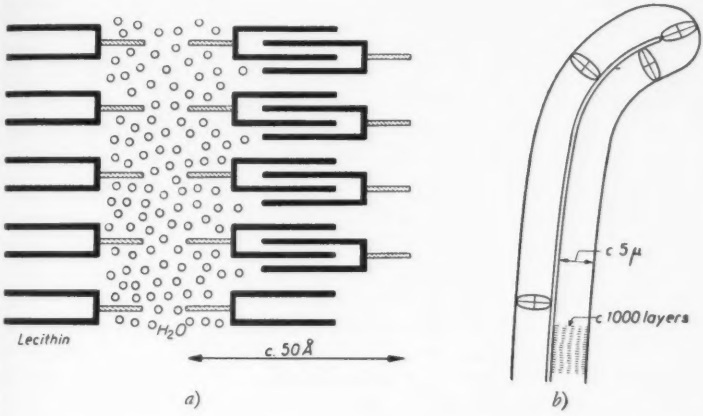

Figure 27. Myelin form of lecithin. (a) *Submicroscopic structure. Hatched, hydrophilic; black, lipophilic part of the fork-shaped lecithin modecule.* (b) *Microscopic image and optics. (Reproduction of figure 47. Frey-Wyssling, A.: Submicroscopic Morphology of Protoplasm. 1953. Courtesy of the Elsevier Publishing Company. Amsterdam.)*

Rinne exposed various pure cerebrosides and phosphatides to water and glycerin-water mixtures and obtained myelin forms similar to those we obtained on exposure of whole brain tissue to surfactants. The myelin forms of pure lecithin shown by Rinne in his figure 10 are strikingly similar to our figures 10 and 11.

It was noted in both guinea-pig and human brain emulsions containing Aerosol OT that myelin forms became elongated and "grew" perpendicular to the striations in Aerosol OT. It appeared that the alignment of molecules of Aerosol OT governed the arrangement of molecules in myelin forms. According to Friedel,[8] many crystals orient mesomorphic substances. When a meso-

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morphic substance is placed on a freshly cleaved crystal plane, it is oriented by this plane so that its optic axis always seems to place itself parallel to the cleavage plane and takes a definite direction relative to the crystallographic axes of its support. Friedel stated further that the mutual orientation is that the two lattices (single or multiple) of the two types of crystals have, within a certain limit of tolerance, the same form and volume; orientation being impossible when the two periods are not properly matched. If one applies the observations of Friedel on mutual orientation of crystals, one may speculate that there is mutual orientation of molecules between Aerosol OT and myelin forms. Myelin forms appear to have the ability to orient the molecular structure of each other as demonstrated by their helical formation when in contact. Myelin forms are similar to liquid crystals in that the molecules must have a chainlike structure, not homopolar but heteropolar; that is, they must contain a hydrophilic and lipophilic pole. In the case of lecithin the hydrophilic group is choline.[2] Tyrosine crystals are apparently formed by the breakdown of proteins of cerebral tissue by the action of the surface-active agent. Tyrosine is relatively insoluble in water and precipitates as crystals. We have demonstrated previously that tyrosine crystals can be formed from leukocytes, liver tissue, cancerous tissue and other tissues by means of a surface-active agent.[9]

Demyelination of the central nervous system is a cardinal feature of many diseases of the brain, many of unknown etiology, such as multiple sclerosis. Surface-active substances will cause breakdown of cerebral lipoproteins with the liberation of lecithin, which in the presence of water develops into myelin forms in vitro. This mechanism of myelin degeneration probably also occurs in vivo, and there is direct and indirect evidence to support this view. Zunz[10] showed that the surface tension of plasma and serum is lowered in dogs and guinea pigs during anaphylactic shock. Weil[11] believed that a surface-active substance derived from the liver is operative in multiple sclerosis, and has produced demyelination in vitro by exposure of nervous tissue to hemolytic surface-active substances as saponin, and sodium taurocholate. Weil and Luhan[12] demonstrated a myelolytic substance in the urine of patients with multiple sclerosis. Von Muralt[13, 14] demonstrated a surface-active substance, related to acetylcholine, formed on excitation of a peripheral nerve. Nageotte[15] described the formation of "ovoids" and "spheres," and the closing of segment of myelin by surface tension in Wallerian degeneration of nerves. In the course of this study I have found myelin forms in acute lesions of multiple sclerosis.

The formation of spiraled myelin forms in surfactant-brain emulsion is of particular interest in view of Steiner's[16] important finding of spirochete-like structures in the brain tissue of patients

with multiple sclerosis. Steiner was of the opinion that he was dealing with a spirochete which he names *Spirochaeta myeloptera,* and it was the etiologic agent of multiple sclerosis. The inference is that Steiner was actually staining spiraled myelin forms which simulate spirochetes and that there is a surface-active substance operative in multiple sclerosis which causes the development of spiraled myelin forms. Steiner described "spirochetes" with a knob on one end and entwined "spirochetes" similar to the helical and knobbed myelin form we have produced chemically.

CONCLUSIONS

1. The addition of a synthetic surface-active agent, dioctyl sodium sulfosuccinate (Aerosol OT), to unfixed human and guinea-pig brain tissue causes the development of myelin forms, cholesterol crystals and tyrosine crystals in vitro. The surface-active agent releases lecithin from cerebral lipoprotein which in the presence of water develops into myelin forms.

2. The addition of distilled water to human brain tissue containing a high concentration of dioctyl sodium sulfosuccinate causes a heavy deposition of cholesterol crystals.

3. The appearance and development of myelin forms under the bright field and polarizing microscopes is described.

4. The direction of "growth" of myelin forms is controlled by dioctyl sodium sulfosuccinate.

5. Helical (spirochete-like) myelin forms develop from brain tissue in the presence of a surface-active substance.

6. Diotyl sodium sulfosuccinate in the gel state when exposed to water develops myelin-form-like structures some of which have a helical appearance.

7. Cationic, ionic, and nonionic surfactants and cobra venom cause the formation of myelin forms from brain tissue.

8. Myelin forms were demonstrated in the acute lesions of multiple sclerosis.

ACKNOWLEDGMENT: I wish to thank Frank D. Nolan, HMC, USN, for valuable suggestions and for technical assistance; and Helen Knight Steward for editorial review.

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Clinicopathologic Conference

Ireland Army Hospital, Fort Knox, Ky.*

WEAKNESS

Summary of Clinical History. A 30-year-old Caucasian woman was admitted to the hospital with the chief complaint of extreme weakness. On the morning of 23 June 1957 she had noted weakness and was unable to stand unassisted. She remained in bed and only arose to take hot baths as treatment, but became progressively worse. On 25 June her husband took her to a civilian physician who noted that she could not hold her head erect, had difficulty in speaking and breathing, and was unable to cough productively.

By occupation the patient was an office worker. Although never constipated, she had taken two or three Ex-Lax tablets daily, and, on occasion, cascara, because she "felt better" after taking them. She had had the usual childhood illnesses without complications and an appendectomy two years prior to the present illness. Six years ago she had been admitted to a hospital because of extreme weakness. There she was told that she had a potassium deficiency and was given fluids intravenously. Response to this therapy was demonstrated by an increase in strength. There had been no other similar episodes until the present illness. The past history was negative for renal disease and urinary tract disorders.

First Hospitalization. The patient was admitted to a civilian hospital on 25 June. Her pulse was slow and irregular, her blood pressure was 130/80 mm Hg., and her temperature was normal.

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Urinalysis was negative except for a trace of albumin. Hemoglobin was 16 grams per 100 ml, and the red blood cell count was 4,630,000 per μl. There were 18,000 white blood cells per μl with 89 per cent neutrophils and 11 per cent lymphocytes. Spinal fluid examination was reported as normal. An electrocardiogram demonstrated flattening of the T waves in the chest leads.

The patient received intravenous fluids with added potassium chloride. Three ampules of Prostigmin (brand of neostigmine) and 0.6 mg of atropine were administered. There was no change in her condition. On the second day of hospitalization, she felt slightly stronger. A roentgenogram of the chest at this time revealed a moderate amount of fluid in the right base. A repeat electrocardiogram showed frequent extrasystoles. The T waves in the chest leads were now upright.

SECOND HOSPITALIZATION

The patient was transferred to this hospital on 26 June.

Physical Examination. The patient's temperature was 97°F; pulse, 60; blood pressure, 120/55 mm Hg.; and respirations were 16. The pupils were constricted but reacted to light. Ptosis of the lids was evident. The lungs were dull to percussion on the right, posteriorly. There were decreased breath sounds in the same area. Frequent cardiac extrasystoles were present. No murmurs were heard. The liver was just palpable below the right costal margin, but nontender; and in the right lower quadrant an appendectomy scar was present. Edema of the extremities was not present, and the peripheral pulsations were good. Hyporeflexia was present bilaterally without pathologic reflexes. A slight brownish discoloration of the skin was noted. There was no increased pigment in the skin folds.

Laboratory Studies. Hematocrit was 43 ml per 100 ml. The white blood cell count was 30,450 per μl with a differential of 89 per cent neutrophils, 2 per cent lymphocytes, 2 per cent monocytes, and 7 band forms. The corrected sedimentation rate was 17 mm per hour. Blood chemistry studies showed the following: serum potassium, less than 2 mEq; serum sodium, 128 mEq; and chlorides, 103.6 mEq; all per liter. Carbon dioxide, 9 millimols per liter; calcium, 9.1 mg per 100 ml; blood urea nitrogen, 43 mg per 100 ml; and creatinine, 7.7 mg per 100 ml. An admission electrocardiograph showed bigeminy from a supraventricular source and low T waves over standard and precordial leads. A roentgenogram of the chest showed a pneumonic consolidation at the right base, with some pleural involvement but without evidence of effusion. The remainder of the chest appeared to be within normal limits. The spinal fluid revealed 4 white blood cells (neutrophils) per μl; glucose, 102.5 mg per 100 ml; globulin,

1 plus; protein, 61 mg per 100 ml; and chlorides, 120 mEq per liter. Urinalysis showed a specific gravity of 1.006, a trace of albumin, and was negative for sugar; there were 6 to 7 red blood cells and 1 white blood cell per high-power field, and amorphous urates.

Course in Hospital. On 27 June fluids intravenously were instituted, with 3,000 ml of 5 per cent dextrose and water containing a total of 60 mEq KCl. This was given in the first 12 hours. By 28 June the patient appeared improved mentally, with some increase in strength but still having respiratory distress. She was taking food and fluids orally. On this date she received 1,000 ml of 5 per cent dextrose in water with 20 mEq of KCl and 2,000 ml of physiologic saline solution, the latter containing 40 mEq of potassium per 1,000 ml. Repeat blood chemistries showed: a blood urea nitrogen of 65 mg per 100 ml; sodium, 134 mEq per liter; chlorides, 102 mEq per liter; carbon dioxide, 9 millimols per liter; and potassium, 1.12 mEq per liter. Repeat urinalysis was unchanged. The patient seemed to improve during the day and appeared stronger. The urinary output during hospitalization had been adequate with from 1,200 to 1,500 ml daily. Potassium by mouth was started on 27 June, and the patient received 20 mg on that day and again on 28 June. A total of 160 mEq of KCl was administered intravenously in a 48-hour period. Subsequent electrocardiograms revealed no significant change despite therapy, except for a decrease in the number of supraventricular extrasystoles. Table 1 summarizes blood chemistry findings. In the early morning of 29 June the patient's condition deteriorated. She had gasping respirations, became unresponsive, and died quietly.

TABLE 1. *Blood chemistry studies*

Chemical constituent	27 June	28 June
Sodium	128 mEq/l	134 mEq/l
Potassium	Less than 2 mEq/l	1.12 mEq/l
Carbon dioxide	9 mM/l	9 mM/l
Chlorides	103.6 mEq/l	102 mEq/l
Blood urea nitrogen	43.05 mg/100 ml	65 mg/100 ml
Creatinine	7.75 mg/100 ml	
Calcium	9.1 mg/100 ml	

DISCUSSION

Doctor Snyder:* My clinical impression when the patient was admitted to the hospital was that this was a case of "potassium-losing" nephritis, secondary to either a chronic glomerulonephritis or chronic pyelonephritis. Terminal azotemia, manifested by an elevated blood

*Capt. Jerone A. Snyder, MC, USA, General Practice Resident.

urea nitrogen and creatinine, was believed to be resultant from the initial disease process.

The complaint of weakness, the presence of hyporeflexia and the electrocardiographic changes reflected the low potassium. The acidosis, low fixed specific gravity, hypokalemia, and hyponatremia seemed to indicate tubular damage. It was thought that the albuminuria and hematuria indicated glomerular damage.

The lack of both a family history and periodicity, along with resistance to intravenous potassium therapy, tended to rule out the diagnosis of familial periodic paralysis. It was evident from the protocol that the possibility of myasthenia gravis was considered. The typical muscular distribution ordinarily demonstrated by this condition was not apparent, however, and this patient showed no response to Prostigmin. Without hypernatremia, hypertension, and alkalosis, a diagnosis of primary aldosteronism must be deleted from the differential. This clinical entity does present hypokalemia that is refractory to potassium therapy, as was noted in this case. Collagen diseases can produce a terminal uremia. However, the general course of the patient was not typical of this group of diseases.

In summary, the hypokalemia, hyponatremia, acidosis, hematuria, albuminuria, and low specific gravity of the urine, together with the physical findings, would indicate primary renal disease.

Doctor Deutsch:* I shall direct the discussion of the differential diagnosis in this case into that derived from the clinical picture and that from the laboratory findings. It will be evident later how these dovetail and help us arrive at a conclusion as to the pathologic entity present.

The prime and most evident sign and symptom is generalized weakness. We can divide the various causes of this finding into several categories. First under consideration would be those diseases of the nervous system producing weakness. Myasthenia gravis produces weakness, but primarily of eyelids and swallowing. Acute infective polyneuritis (Guillain-Barré syndrome) gives generalized weakness but usually with sensory changes. Poliomyelitis, of course, must be considered. The usual picture of headache, stiff neck and patch involvements was not evident here. Progressive muscular atrophy and amyotropic lateral sclerosis produce weakness but with different distributions of involvement, sporadic remissions, and exacerbations.

The next group of causes of extreme weakness are the infections. Of course, this overlaps with the previous group since infections of the nervous systems include both groups. Poliomyelitis is one. Meningitis is another, either purulent or aseptic. The stiff neck, headache, and fever usually present in meningitis were absent here. Varieties of encephalitis can readily be excluded. Of course, a normal spinal

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tap is of utmost importance in ruling in or out the diseases of this group.

Chemical or toxic causes for weakness, as in lead poisoning, are next to be considered. This is usually an isolated nerve paralysis such as of the ulnar or peroneal nerve. Tick paralysis can be included in this group. No ticks (or history of same) were present. A history of methyl alcohol ingestion was not elicited. Arsenic poisoning can give peripheral neuritis, but usually with sensory changes. The next group to be included are the metabolic diseases. These would produce weakness through the production of low potassium level. This would include Addison's disease, Cushing's disease, familial periodic paralysis, and diabetic acidosis. In this case, none of these fit except, as we shall see shortly, that a low potassium level was present. Another important but rare cause would be "potassium-losing" nephritis. Other possibilities include primary aldosteronism, which gives a low potassium but high sodium level, plus hypertension and edema, and treatment with steroids must be mentioned. Of course, chronic diarrhea is another factor to be considered in low potassium levels.

Much of the differential diagnostic possibilities mentioned can be ruled out immediately by the laboratory findings. Thus, the normal findings in spinal fluid examination would tend to eliminate infections such as poliomyelitis, encephalitis, and myelitis, as well as polyneuritis. The normal sodium level eliminates Cushing's disease and aldosteronism. The most significant laboratory findings are the low potassium, high creatinine, elevated blood urea nitrogen, low CO_2, and albuminuria. These certainly all point to kidney disease. I can't think of any other cause for elevated creatinine than kidney disease. This, plus the other evidence of mild acidosis, albuminuria, and urea nitrogen retention, indicate a very significant degree of kidney failure. Although a low potassium level as a result of potassium-losing nephritis is rare, it has been reported and seems to be a recognized entity. Without balance studies it is difficult to say if the patient was in negative potassium balance, but I believe it is a safe assumption to make. It also is most difficult to make an accurate determination as to the type of kidney disease present inasmuch as all of the various chronic nephritides can produce the same end picture, whether it is chronic glomerulonephritis or chronic pyelonephritis. If it were necessary to make a choice, the absence of hypertension, edema, and episodes of acute nephritis make one lean toward chronic pyelonephritis as the choice.

What was the role of the chronic use of laxatives in her death and the mechanism of death? I don't believe she died in uremia. I believe she died of potassium depletion with cardiac arrhythmia resulting therefrom. This has been discussed in an excellent paper by Relman and Schwartz,[1] in which they pointed out the tubular abnormalities that had appeared in people who took cascara or laxatives containing aloin or phenophthalein for prolonged periods of time, and stated that

patients with chronic diarrhea from other causes such as ulcerative colitis and regional enteritis had suffered potassium depletion. Renal biopsies showed the tubular changes which they attributed to this low potassium level.

Now if we can visualize an already significantly damaged kidney losing potassium, as in this case, then have superimposed on it the additional insult of low potassium effect on the tubules with further damage and further loss of potassium, there was then reached a point where the potassium level declined to the point at which cardiac arrhythmia and/or standstill occurred.

Doctor McNerney: I would like to interject a few remarks concerning the possible basic renal lesion which existed in this patient. The excellent differential discussed by Captain Snyder in his presentation and by Colonel Deutsch leaves little room for doubt that this entity of low potassium and sodium levels, along with elevated blood urea nitrogen and creatinine in an acidotic patient, is renal in origin.

The kidneys, as noted at autopsy, definitely resembled the scarred kidneys of chronic glomerulonephritis. In retrospect, a review of this patient's history does not follow the course one would expect in this disease. Here we have a patient with renal disease of at least six years' duration—if we accept the previous episode as being related, and I believe we must. This implies the presence of some renal disease even prior to this. In light of this thought, the absence of episodes of edema, hypertension, or even clinical symptoms necessitating the seeking of medical advice during all these years, is quite unusual for a patient with chronic glomerulonephritis.

For these reasons, I would prefer to entertain the idea that the basic pathologic condition in the kidneys will more probably be chronic pyelonephritis. This is a disease that is common in this sex, need not produce significant clinical symptoms and, in fact, can be mildly present in the absence of laboratory findings such as proteinuria and positive culture.

In addition, there have been experimental studies as well as a few case reports where the excessive use of laxatives resulted in low potassium levels to a clinically significant degree. This has produced reversible renal changes of a hydropic nature in the proximal convoluted tubules. This patient was a chronic laxative user.

In summary, I believe this patient had chronic pyelonephritis which was further insulted by a low potassium resulting from excessive use of laxatives and as a result died an electrolyte death despite attempts at restoration of potassium.

Doctor Carrasco:* In a child a similar clinical and laboratory picture would necessitate investigation for the possibility of poisoning, with

*Lt. Col. Enrico Carrasco, MC, USA, Chief, Pediatrics Service.

particular emphasis upon possible arsenical nephropathy. Another disease of the nervous system producing weakness in a child, is the rare disorder of amyotonia congenita. In most cases the picture of hypotonia and cardiac arrhythmia is found in hypokalemia resulting from chronic diarrhea. However, in the case under discussion I concur with the discussants' impression.

Dr. Snyder's diagnosis:
Primary renal disease

Dr. Deutsch's diagnosis:
Chronic pyelonephritis with potassium depletion and cardiac arrhythmia

Dr. McNerney's diagnosis:
Chronic pyelonephritis with potassium depletion caused by laxatives.

PATHOLOGIC FINDINGS

Doctor Fadell:* At autopsy there was bilateral hydrothorax of approximately 1,000 ml each. The heart weighed 320 grams and showed no evident dilatation or other abnormalities grossly or microscopically. Both lungs were heavy, and sectioning revealed a large amount of frothy, sanguineous edema fluid. The right kidney weighed 150 grams and the left kidney weighed 140 grams. The capsules stripped with slight difficulty to reveal a rather pronounced diffuse hemorrhagic discoloration, presumably due to cortical hyperemia rather than to petechiae. A diffuse granularity was present bilaterally. There was poor distinction between cortex and medulla with thinning of the cortical portions. The pyramids appeared pale. The pelves were not dilated and the ureters communicated normally with the urinary bladder and showed no dilatation.

Microscopically (figs. 1 and 2), the kidneys showed moderate, inactive pyelonephritis with chronic inflammatory infiltrates and associated cortical linear scarring. Medullary intertubular scarring and foci of calcification were present. Acute tubular degenerative changes with regeneration were widespread. Periglomerular fibrosis and fibrous obliteration of glomeruli were seen. In some areas entirely intact glomeruli were seen together with intact tubules. These areas seemed to alternate with involved areas.

The right ovary was partially replaced by a cyst which measured 1.5 by 1 cm. Sectioning revealed the contents of the cyst to be clear fluid with the cyst wall being yellow and convoluted. Microscopic study showed this to be a corpus luteum of pregnancy. Sectioning into the uterus revealed the fundic portion to be filled with a friable, polypoid material. Microscopic study showed products of conception. The adrenals had no cortical adenomata or nodularity. They were not en-

*Lt. Col. Edward J. Fadell, MC, USA, Chief, Laboratory Service.

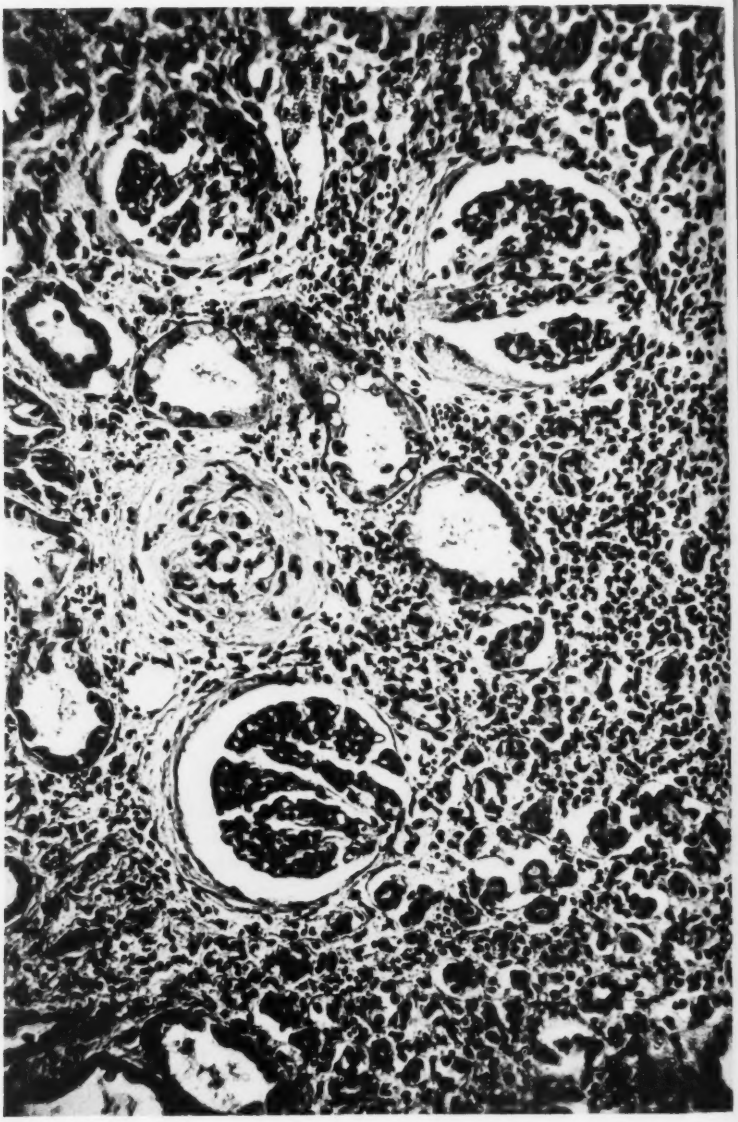

Figure 1. Photomicrograph of section of kidney showing periglomerular and glomerular fibrosis, interstitial chronic inflammation, and tubular atrophy. (× 130)

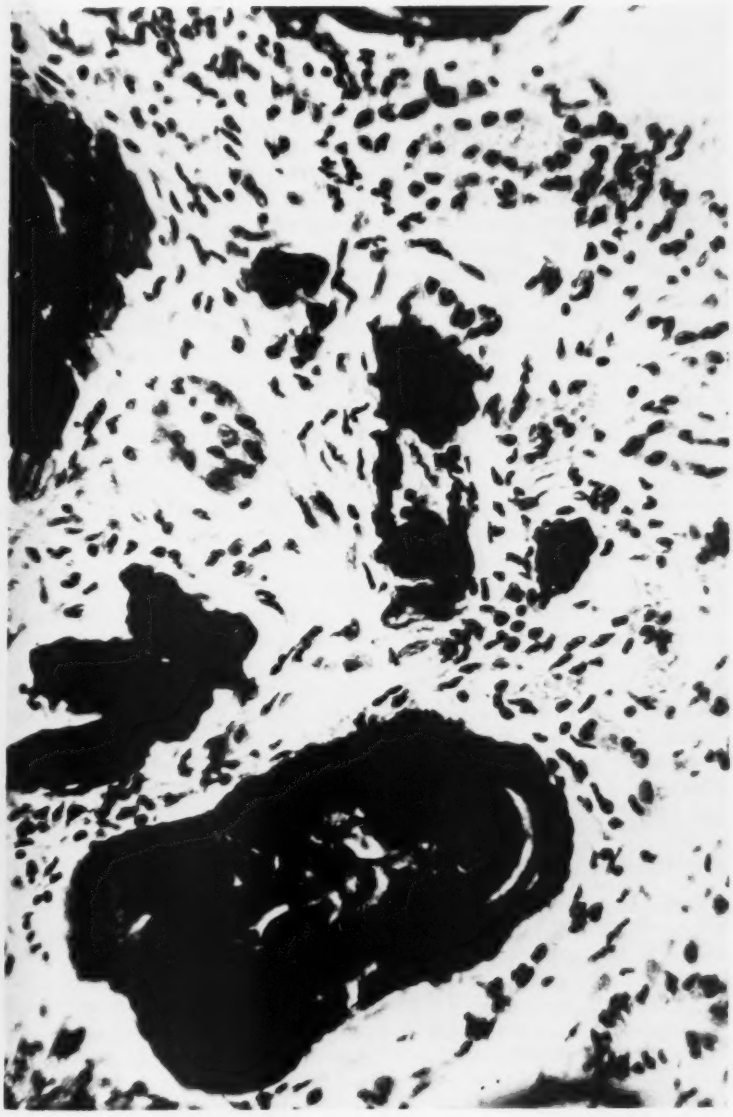

Figure 2. Photomicrograph of section of kidney showing tubular atrophy and calcification. (× 260)

larged, weighing 12 grams together. Histologic study revealed only moderate lipid depletion with no evident hyperplasia. A terminal bronchopneumonia was present.

The cause of death was hypokalemia with the associated cardiac functional impairment. The anatomic defect in the kidneys seems best designated as a pyelonephritis. The cause of the hypokalemia, at first glance, seems related to the renal pathology, with the condition being such as to constitute an example of "potassium-losing" nephritis. Such cases have been reported recently,[2,3] and especially in the British literature. However, renal loss of potassium of such magnitude as to result in the low potassium syndrome is considered quite rare. Unfortunately, urinary potassium studies were not performed. The renal conditions in which a low serum potassium have been encountered not infrequently are the Fanconi syndrome and the Albright-Lightwood syndrome. However, these conditions can be readily excluded in that the latter situation generally shows a hyperchloremia, and, in the case of the Fanconi syndrome, the clinical and laboratory findings are characteristic. It is possible that some of the reported cases of "potassium-losing" nephritis may actually represent primary aldosteronism. This seems excluded in this instance on the basis of lack of inciting adrenal pathology. It should be emphasized that potassium depletion in itself may give rise to renal dysfunction. A specific lesion not infrequently can be demonstrated either on biopsy or at autopsy in instances of hypokalemia. In this condition extensive hydropic changes may be seen within the renal tubules. Although the possibility of a true "potassium-losing" nephritis cannot be excluded in this case, the history given by the patient of excessive laxative ingestion raises the possibility that rather than a renal loss of potassium, loss may have resulted from a chronic diarrhea secondary to the stated laxative ingestion. This would explain the hypokalemic episode six years previously. The reported cases have not shown the severe renal functional impairment as noted in this case, however. It is quite possible that in this case some renal dysfunction was due to a potassium loss in the stool, which together with the pre-existing renal disease may have resulted in the progressive renal impairment noted.

Pathologic diagnoses:

1. Hypokalemia from renal and enteric potassium depletion
2. Chronic pyelonephritis

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SERVICE ARTICLE

STREPTOCOCCAL PROPHYLAXIS IN NAVY RECRUITS WITH ORAL AND BENZATHINE PENICILLIN

PAUL F. FRANK, M. S.

EXPERIENCE with penicillin prophylaxis against streptococcal infections has shown that the administration of 157 mg (250,000 units) of buffered oral penicillin G twice daily for a period of 10 days is effective in disrupting streptococcal epidemics among recruit populations.[1] Recently, however, a severe streptococcal epidemic that occurred at this training center required two such courses of penicillin before it was brought under control.[2-4] There were two basic reasons for this: (1) The initial course of penicillin was not sufficient to eradicate the carriage of the epidemic strain in such a heavily infected population; and (2) there were enough individuals who did not receive penicillin prophylaxis, either because of hypersensitivity to penicillin or for administrative reasons, to act as a reservoir for reseeding the population.

Since the use of long-acting benzathine penicillin was proved to be effective in the control of streptococcal infections among rheumatic fever patients,[5] its prophylactic application among military personnel has been given a limited trial.[4,6-7] In an early investigation in a military population, however, a rather high incidence of hypersensitivity reactions was encountered,[6] and mass prophylaxis in recruit populations has not been attempted until recently.

The present investigation was undertaken for two reasons. First, an adenovirus vaccination study was being conducted in the recruit population at this naval station, and some form of penicillin prophylaxis was mandatory to control streptococcal disease in order that a valid evaluation of the vaccine program could be made. Second, a limited amount of benzathine penicillin was available for trial, and it was desirable to control streptococcal carriage among new men arriving for training. This was necessary during and for a period subsequent to an oral peni-

From Research Project NM 52 06 04, Division of Bacteriology, U. S. Naval Medical Research Unit No. 4, Great Lakes, Ill.

cillin prophylactic program among onboard recruits, to prevent any recurrence of a streptococcal epidemic at the conclusion of oral penicillin prophylaxis.

This report includes observations on streptococcal prevalence before, during, and subsequent to the institution of penicillin prophylaxis; on the distribution of the two different penicillin preparations among the recruit population, and the proportion of recruits under effective prophylaxis at any one time during the study; on the incidence of isolation of beta hemolytic streptococci among men receiving either penicillin preparation during the various periods of the study, and the time when men previously protected with benzathine penicillin acquired group A streptococci; and on the incidence and severity of hypersensitivity reactions resulting from the use of the oral or benzathine penicillin preparations.

MATERIALS AND METHODS

Penicillin Prophylactic Program

Penicillin prophylaxis consisted of two different types of penicillin, administered by two different routes. From 18 January to 27 April 1956, all recruits reporting aboard this training center who denied allergy to penicillin were given a single, intramuscular injection of 495 mg (600,000 units) of benzathine penicillin in the buttocks within four to five days after arrival. The penicillin was given at the time of adenovirus vaccination and the first series of routine immunizations.

Recruits already in training who did not claim hypersensitivity to penicillin, including those in preparatory school, detention and reassignment companies, brig, and medical and dental holding companies, received, for a 10-day period beginning 23 January, 157 mg (250,000 units) of buffered oral penicillin G twice daily (before breakfast and before the evening meal). For an additional 30-day period ending 3 March, or until termination of training, whichever occurred first, the dose was reduced to once daily. All penicillin tablets were distributed by the Medical Department under the supervision of the Senior Medical Officer to the training regiments, where the tablets were issued to the company commanders for administration to the recruits. Any recruit claiming a history of hives or allergy to penicillin was required to report to one of the field dispensaries, where he was examined by a medical officer and excused from the program if the claim was substantiated.

Collection of Material To Be Used in the Evaluation

Bacteriological cultures. Throat cultures for the isolation of beta hemolytic streptococci were collected from recruits examined in the barracks during weekly surveys for the incidence of re-

spiratory illnesses. Companies representative of each week of training were chosen at random so that approximately one fifteenth of the training regiment was sampled weekly. In addition, daily throat cultures were taken on recruits reporting to sick bay with febrile respiratory illnesses. The cultures were seeded on sheep-blood agar plates and examined for the presence of beta hemolytic streptococci. All streptococcal strains isolated were identified serologically as previously described.[6]

Penicillin reactions. During the period of penicillin prophylaxis, any recruit presenting himself to the regimental infirmary with symptoms of penicillin hypersensitivity was examined by a medical officer. He completed a questionnaire on all reactions seen, recording the type of penicillin given, the interval between injection and appearance of symptoms, the symptoms encountered, and the relative severity of the reaction.

Rheumatic fever. Only confirmed cases of rheumatic fever among recruits in training were tabulated in this study.

RESULTS

Prior to the beginning of penicillin prophylaxis, the respiratory disease admission rates rose from 8 per 1,000 per week on 3 December to 15 per 1,000 per week on 31 December and returned to about 7 per 1,000 per week around 14 January (fig. 1). The isolation of group A streptococci from recruits with respiratory

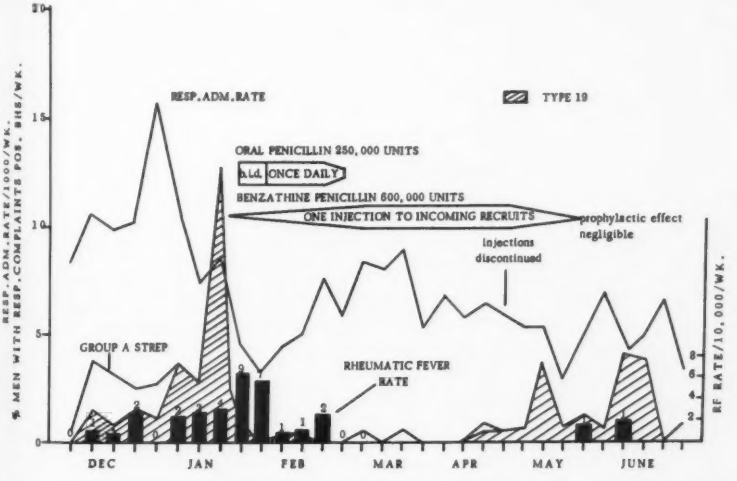

Figure 1. Incidence of streptococcus isolation, rheumatic fever, and hospital admissions for acute respiratory diseases during oral penicillin or benzathine penicillin prophylaxis, winter of 1955-1956, Great Lakes, Ill.

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disease complaints seen in the barracks did not exceed 4 per cent. However, during this time large muco-matt strains of type 19 streptococci were being recovered. During the second week in January both respiratory disease admission rates and streptococcal isolation rates began to climb, the latter at a greater rate. At this time four cases of rheumatic fever were reported at the hospital. On the strength of the increase in streptococcal isolations, the occurrence of rheumatic fever, and the prevalence of a single type of streptococci that exhibited muco-matt colonies on blood agar plates so characteristic of epidemic streptococci, penicillin prophylaxis was instituted on 18 January.

During the period of prophylaxis, respiratory disease admission rates ranged between a low of 3 per 1,000 per week in early February to a high of 9 per 1,000 per week in the third week of March. Group A streptococcal isolations during this period were negligible, and only toward the end of the prophylactic period did the streptococcal isolation rates begin to increase, fluctuating between 1 and 4 per cent through May and June. Most of these isolations were type 19.

The prevalence of beta hemolytic streptococci in the recruit population prior to penicillin prophylaxis is reflected not only in the sharp rise in streptococcal isolation rates, but also in the high incidence of rheumatic fever (20 cases) occurring in the five-week period following the beginning of prophylaxis (fig. 1). In addition, in the two weeks just prior to prophylaxis, six cases of scarlet fever were reported among the recruits. Similarly, the evidence of a small outbreak of streptococcal infections in the last week of April and first week of May was evident in the appearance of two additional cases of rheumatic fever and two cases of scarlet fever.

In any penicillin prophylactic program, there will be a few individuals who will not be able to participate in the program because of hypersensitivity to penicillin. In addition, there will be others who will not receive prophylaxis for administrative reasons or who will not be under effective prophylaxis due to the expiration of the prophylactic action of the penicillin preparation under investigation. Figure 2 shows the percentage of recruits under effective penicillin prophylaxis at any one time during the study period. Early in the program, about 15 per cent were not given any penicillin. These men had less than 10 days of training left and would not have received the full 10 days of oral prophylaxis. Subsequently, for a period of about three weeks, approximately 98 per cent of the recruits were under effective penicillin prophylaxis. During the month of February, the proportion of men receiving the oral preparation declined from 85 to 35 per cent, while those men under effective benzathine penicillin (21 days or less) increased to 42 per cent. During this

time, the percentage of men not under effective treatment increased from 5 to about 20 per cent. Upon discontinuation of oral prophylaxis in the week of 7 March, from 23 to 35 per cent of the recruit population remained under effective prophylaxis until May.

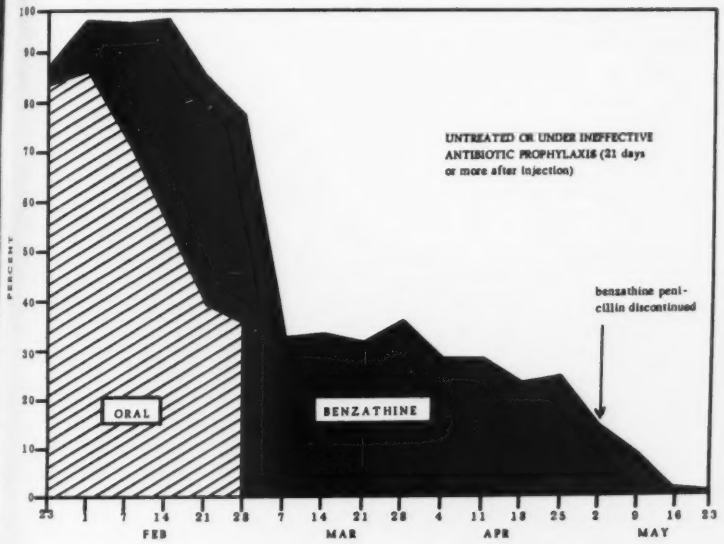

Figure 2. Percentage of recruit population under effective antibiotic prophylaxis during the period of administration of oral or benzathine penicillin, 19 January to 23 May 1956.

Bacteriological Data

Because there existed a period during this study when both oral and benzathine penicillin were being administered, another period when only benzathine penicillin was used, and a period following the discontinuance of all prophylaxis, bacteriological data are presented separately for each of the three periods.

Table 1 summarizes the recovery of beta hemolytic streptococci from throat cultures of 2,025 men in companies receiving oral penicillin prophylaxis, and of 998 men in companies receiving benzathine penicillin prophylaxis. It also shows the percentage of recruits excluded from penicillin prophylaxis because of hypersensitivity to penicillin or because they were transferred into a training company during the prophylactic program from a source where they had not received prophylaxis. It will be noted that a history of previous penicillin reaction was about twice as high in the benzathine group (4.5 per cent) as in the group treated with oral penicillin (2.2 per cent). Although the prevalence of

TABLE 1. *Isolation of beta hemolytic streptococci from Navy recruits receiving oral penicillin G or benzathine penicillin in the period 23 January through 3 March 1956*

	Companies receiving oral penicillin		Companies receiving benzathine penicillin	
	Number	Per cent	Number	Per cent
	Men excluded from prophylaxis			
Penicillin sensitive	44	2.2	45	4.5
Number positive	5	11.4	2	4.5
Number group A	3*	6.8	0	0
Miscellaneous reasons	-	-	136	13.6
Number positive	-	-	9	5.9
Number group A	-	-	0	0
Subtotal	44	2.2	181	18.1
	Men receiving prophylaxis			
Number cultured	1981	97.8	817	81.9
Number positive	47	2.4	11	1.3
Number group A	8**	0.4	1***	0.1
Total cultured	2025		998	

*Type 19
**Seven of these strains were type 19
***Type 5 strain isolated 8 days after receiving benzathine penicillin

streptococcal positive throat cultures was about the same among men receiving either penicillin preparation, group A strains of the epidemic type were found only among companies receiving oral penicillin, where a rate as high as 6.8 per cent of uninoculated men carried this type. The single isolation of a group A strain among the benzathine penicillin-treated companies occurred in a recruit who had received his injection 8 days before; however, this strain proved to be type 5. Many of the non-group A strains isolated during this period among penicillin-treated men were minute group G. One additional fact deserving attention is that approximately 18 per cent of the men in the benzathine penicillin-treated companies did not receive prophylaxis during the period of combined oral and benzathine prophylaxis.

Data on the results of the second period of study, when only benzathine penicillin was given to the recruits arriving for training, are shown in table 2. Cultures for the isolation of beta hemolytic streptococci were obtained from 4,203 men, only 2.8 per cent of whom claimed penicillin hypersensitivity. An addition-

al 6.6 per cent were excused from prophylaxis for administrative reasons. The total percentage of men not receiving prophylaxis during this period was approximately one half that in the previous study period.

TABLE 2. *Isolation of beta hemolytic streptococci from Navy recruits among companies receiving benzathine penicillin in the period 4 March through 27 April 1956*

	Cultured		Positive		With group A streptococci	
	Number	Per cent	Number	Per cent	Number	Per cent
	Receiving no penicillin					
Penicillin sensitive	119	2.8	5	4.2	1	0.8
Others	279	6.6	5	1.2	2	0.7
Subtotal	398	9.4	10	2.5	3*	0.8
	Receiving benzathine penicillin					
	3805	90.6	87	2.3	6**	0.2
Total	4203	100	97	2.3	9	0.2

*Two type 19 isolations.
**Four type 19 and two type 5 isolations. All isolations 29 days or more after receiving benzathine penicillin.

Although the recovery of beta hemolytic streptococci among men receiving penicillin prophylaxis was the same as among those not receiving prophylaxis, there were significantly fewer isolations of group A strains in the treated recruits. Actually, all the group A strain isolations from the treated men occurred 29 days or more after receiving benzathine penicillin prophylaxis. Type 19 strains were being isolated from the treated as well as the untreated recruits during this period of the study.

Following the administration of benzathine penicillin prophylaxis, an additional two-month period of observation was undertaken. The streptococcal isolation rates are shown in table 3. During this period, about one third of the recruits came from companies that had received benzathine penicillin prophylaxis upon arrival at this station. As can be seen, group A type 19 isolations were approximately the same among recruits from treated and untreated companies.

One of the basic issues in any penicillin prophylactic program, particularly in the case of a depot type penicillin, is the experience of the treated companies during the period when the

protection of the penicillin has been exhausted. To shed some light on this question, cultural data from companies in their first four weeks of training were compared with that of companies in their fifth through ninth week of training for each of the three study periods. It was assumed that the protective effect of penicillin was minimal after 4 weeks. During each of the study periods, a comparison was made between those men receiving or not receiving prophylaxis (table 4).

TABLE 3. *Isolation of beta hemolytic streptococci from Navy recruits in the period following discontinuance of benzathine penicillin prophylaxis, 28 April through 30 June 1956*

	Benzathine penicillin-treated companies			Untreated companies
	Treated	Untreated		
		Penicillin-sensitive	Other	
Number positive	70	0	2	94
Per cent positive	5.3	0	13.4	4.2
Group A				
Number	21*	0	1*	24*
Per cent	1.6	0	6.7	1.1
Number cultured	1333	15	15	2267

*Type 19

In the period of oral prophylaxis there were no significant differences in group A isolation rates between the early and late training periods from recruits receiving or not receiving benzathine penicillin. It should be remembered that during this period 80 to 95 per cent of the recruits were under effective prophylaxis. Similarly, there was no apparent increase in group A acquisitions among treated men in the later periods of training when only benzathine prophylaxis was given. However, recruits in the benzathine-treated companies who did not receive the antibiotic did exhibit an increase in streptococcal acquisitions in the fifth to ninth week of training. During this period, only 23 to 35 per cent of the recruits were under effective penicillin prophylaxis.

In the four weeks following discontinuance of benzathine penicillin prophylaxis of arriving recruits, from 2 to 15 per cent of the recruit population was under effective treatment. As can be seen, the effect of benzathine penicillin is manifested only in the first four weeks of training. Streptococcal acquisitions became significantly increased in the latter half of training in both treated and untreated men.

TABLE 4. *Comparison by periods in training of the incidence of isolation of group A streptococci among recruits in companies with or without benzathine penicillin prophylaxis, during and following discontinuance of such prophylaxis*

	Weeks of training					
	First to fourth week			Fifth to ninth week		
	Cultured	Group A isolations		Cultured	Group A* isolations	
	Number	Number	Per cent	Number	Number	Per cent
	Period of oral penicillin prophylaxis					
Received benzathine	776	1	0.1	41	0	0
No treatment	166	0	0	15	0	0
	Post oral prophylaxis period					
During benzathine prophylaxis						
Treated	1911	3	0.2	1894	3	0.2
Untreated	129	0	0	269	3	1.1
Post benzathine prophylaxis						
Treated	254	1	0.4	1079	20	2.0
Untreated	1499	11	0.7	768	13	1.7

*Ninety per cent of group A streptococci isolated were type 19.

In connection with an adenovirus vaccine study conducted concurrently with the penicillin prophylactic program, cultures from 1,688 recruits coming to the sick bay with febrile respiratory disease complaints were examined for the presence of beta hemolytic streptococci during the period of 17 March through 12 May. During the period of benzathine penicillin prophylaxis, an average of 3.6 per cent of the recruits from whom cultures were obtained exhibited positive culture for group A beta hemolytic streptococci (table 5), and all but two of the strains proved to be type 19. This would indicate that up to 3.6 per cent of the men reporting to the dispensary with febrile respiratory illnesses possibly were suffering from streptococcal infections. However, about one fifth of the 61 men with positive cultures did not receive prophylaxis.

Acquisition of Group A Streptococci by Benzathine-Treated or Untreated Recruits

An important factor in the effectiveness of the penicillin prophylactic program, in addition to the eradication of the beta hemolytic streptococcus from the nose and throat, is the period an individual is protected against the acquisition of streptococci. During this study, there were available isolations of group A streptococci from recruits receiving the single injection of 495 mg (600,000 units) of benzathine penicillin and isolations from those not receiving prophylaxis. The distribution of these isolations in days after injection or days aboard, respectively, is depicted

TABLE 5. *Incidence of group A streptococci among recruits reporting to sick bay with febrile respiratory complaints for six weeks during and two weeks after benzathine penicillin prophylaxis*

Week ending	Number cultured	Men receiving prophylaxis			Men receiving no prophylaxis	Total	
		Number Group A	Days since injection		Number Group A	Group A	
			Mean	Range		Number	Per cent
During prophylaxis							
3/24/56	280	9	51.8	27-67	4	13	4.6
3/31/56	286	2	48.0	44-52	0	2	0.7
4/7/56	254	4	50.5	31-66	1	5	1.9
4/14/56	238	8	52.0	36-62	3	11	4.6
4/21/56	210	8	53.0	33-64	0	8	3.8
4/28/56	158	9	55.0	46-68	3	12	7.6
After prophylaxis							
5/5/56	149	4	58.2	52-65	0	4	2.7
5/12/56	113	3	66.6	66-68	1	4	3.5
Total	1688	47	54.3	27-68	12	61*	3.6

*Ninety-seven per cent of these strains were type 19.

in figure 3 as accumulative per cent and number of acquisitions per week. Acquisitions of group A streptococci among benzathine-treated recruits were significantly delayed as compared to the untreated controls. Except for one acquisition between the sixth and the tenth day, protection with a single dose of benzathine penicillin was extended to 28 days or more. The period where the slope of the curve or the number of acquisitions among treated men is the greatest occurred between the 46th and 65th day after injection of penicillin, during which time approximately 50 per cent of the 75 acquisitions had occurred.

Additional data on the acquisition of streptococci by benzathine-treated recruits were obtained on those recruits reporting to the infirmary with febrile respiratory complaints. Again referring to table 5, it can be seen that the acquisitions took place, on the average, 54.3 days after receiving the benzathine penicillin injection.

Untoward Effects of Oral and Benzathine Penicillin Prophylaxis

During this investigation, approximately 26,000 recruits received some form of penicillin. Of these, one half were given benzathine penicillin. Only 0.4 per cent of the benzathine-treated recruits and 0.07 per cent of those receiving oral penicillin G developed hypersensitivity that required admission to the hospital. No anaphylactoid reactions were observed. From both clinical impressions and recorded symptomatology, it appeared

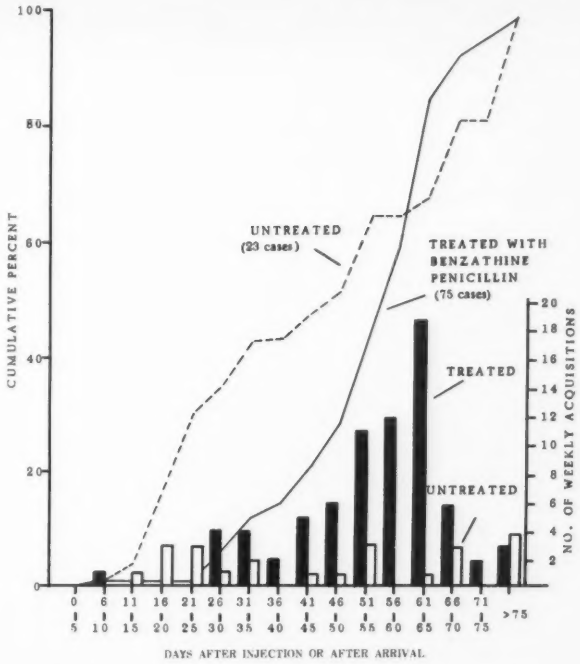

Figure 3. Time of acquisition of Group A streptococci by those recruits treated or untreated with benzathine penicillin, winter of 1955-1956.

that reactions to benzathine penicillin were more severe than from the oral preparation (table 6). In addition, approximately 86 per cent of those who reacted to oral penicillin G and 60 per cent of those reacting to benzathine penicillin responded to outpatient therapy. The only other side effect experienced by the recruit was severe local pain at the site of injection for a period ranging from 1 to 3 days. No sterile abscesses were encountered.

Figure 4 shows the relationship of time of injection of benzathine penicillin or starting of oral prophylaxis until the manifestation of symptoms of hypersensitivity. The number of cases of hypersensitivity among men receiving the oral preparation occurred at a uniform rate during the first 20 days of prophylaxis, during which time 80 per cent of the reactions had taken place. An occasional reaction was observed as long as the 40th day following the beginning of prophylaxis. Reactions of men treated with benzathine penicillin occurred most frequently between the 8th and the 14th day following injection. About two thirds of the cases reported to sick bay during this period. Only a few reactions were observed beyond the 15th day, two occurring 51 and 52 days,

respectively, following inoculation. A search of the medical record of these two men failed to indicate that any additional penicillin had been received.

TABLE 6. *Penicillin reactions among Navy recruits receiving oral or benzathine penicillin prophylaxis*

	Oral		Benzathine	
	Number	Per cent	Number	Per cent
Men with reactions	65	0.51	129	1.1
Men receiving prophylaxis	12,707		13,549	
	Reaction symptoms			
Urticaria	51	83.7	114	93.5
Angioneurotic edema	4	6.6	21	17.2
Joint pain	8	13.1	34	27.9
Total classified	61		122	
	Severity of reaction			
Clinical impression				
Mild	39	66.2	52	42.6
Moderate	19	32.4	64	52.5
Severe	1	1.7	6	4.9
Total classified	59		122	
Hospitalizations	9	13.8	53	41.4
Hospitalizations (of total treated)	9	0.07	53	0.39

Seven additional cases could not be classified, as the recruits received both preparations or subsequently received an injection of procaine penicillin before onset of symptoms.

DISCUSSION

From the over-all picture depicted in figure 1, it appears that the prophylactic use of oral penicillin G and benzathine penicillin was effective not only in disrupting a streptococcal disease outbreak among the recruit population, but also in keeping the isolation rate of group A beta hemolytic streptococci at a minimum during the winter of 1955 and 1956. On the other hand, in spite of the rather intensive penicillin prophylactic program, there appeared to have been a recrudescence of the outbreak during April, May, and June, just before benzathine prophylaxis was discon-

tinued. The same type of streptococci was isolated during this period and two cases each of rheumatic fever and scarlet fever appeared, suggesting that this strain was similar to or the same as that isolated earlier in the year, and that eradication of the source of epidemic streptococci was not accomplished.

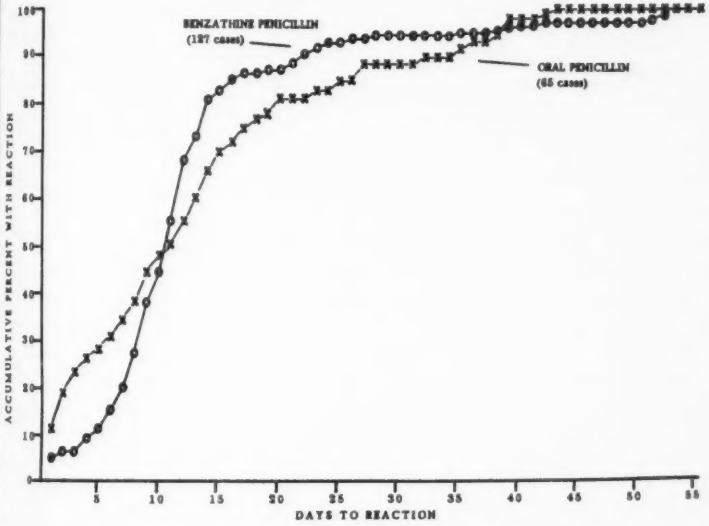

Figure 4. Days to onset of symptoms of penicillin hypersensitivity reaction in recruits receiving oral or benzathine penicillin.

This reappearance of the outbreak could have resulted from (1) carriage of the epidemic strain among individuals not receiving penicillin prophylaxis, who acted as a nucleus for the spread of streptococci when prophylaxis was terminated; (2) unsuccessful eradication of the epidemic strain among men receiving treatment, who also were a source of epidemic streptococci in the post-prophylactic period; and (3) perpetuation of the strain among benzathine penicillin-treated men who acquired, in their later weeks of training when the protective antibiotic levels in the blood had been dissipated, epidemic streptococci from untreated or treated recruits carrying the strain.

It was seen that in both the oral penicillin- and benzathine-treated companies, there was a proportion of the men who did not receive penicillin prophylaxis, reaching as high as 18 per cent in the benzathine-treated companies. Although isolations of group A streptococci were not excessive in these men, the presence of type 19 streptococci may ultimately have been responsible for the subsequent streptococcal outbreak.

It also is conceivable that the prophylactic program may have failed to eradicate group A streptococci from the recruits treated orally with penicillin, as suggested by the fact that 0.4 per cent of the cultures taken from these men yielded type 19 streptococci during the 40-day period. There is some reason to believe that the appearance of type 19 streptococci in orally treated men may also have been due to lapses in administration of the program. Not infrequently on interrogation, rheumatic fever patients reported a break in the daily administration of the penicillin tablets. On the other hand, it is quite unlikely that failure to eradicate can explain the appearance of type 19 streptococci in the benzathine-treated men, because with the exception of the one positive culture 5 days after the man received his benzathine penicillin injection, no other positive cultures were obtained until after 28 or more days (tables 2 and 5, and fig. 3).

This then brings us to a third possible explanation for the reappearance of the epidemic strain; namely, the perpetuation of the epidemic strain in the benzathine-treated companies in their later weeks of training, when penicillin levels were below that necessary to prevent acquisition of beta hemolytic streptococci. In previous studies conducted among recruits at this training center, it has been observed that the greater frequency of isolation of group A streptococci and the increase in incidence of streptococcal disease have occurred among companies in their later weeks of training.[9,10] In addition, it was shown that if even as high as two thirds of the recruit company were protected by antibiotic prophylaxis against streptococcal disease, the streptococcal carriage in a placebo-treated group was sufficient to result within a three-week period in as high a streptococcal recovery rate in the previously protected men as in the placebo group.[10] In the present study a similar situation is encountered where, after the initial protection period of approximately 4 to 5 weeks, the treated men begin to acquire group A streptococci, especially when the proportion of the recruit population under effective benzathine prophylaxis was declining in the post-prophylaxis period. Just what would have developed from the outbreak if the summer season had not arrived, is debatable.

It seems quite certain that the prophylactic use of oral penicillin in the onboard recruit population in conjunction with the prophylactic use of benzathine penicillin in incoming recruits effectively prevented a major outbreak of streptococcal infections among the recruits in the winter of 1955-1956. However, it is not expected, for several reasons, that such a program would be generally accepted as a means of continually controlling streptococcal disease in other recruit populations. In the first place, it is not feasible to institute a daily oral penicillin prophylactic program of longer than 10 days, because the line personnel who administer the antibiotic become apathetic to the program. This then leads

to breakthroughs in the program with subsequent failure to eradicate the epidemic strain from the recruit population. Evidence of such breakthroughs was brought to light in this study on routine interrogation of rheumatic fever patients admitted to the hospital. In the second place, because of the ease of administration and long periods of prophylactic activity of a single injection of benzathine penicillin, a prophylactic program employing this type of penicillin would be much more advantageous.

It was shown in this study that 495 mg (600,000 units) of benzathine penicillin afforded, with the exception of one case, a minimum period of 28 days of protection, and it was not until about the 50th day after injection that the protective effect appeared to have been expended. Other studies conducted in the Armed Forces have reported breakthroughs much earlier than this;[4,6,7] however, in most instances such studies were instituted at a time when streptococcal infections were prevalent or of epidemic proportions. Although streptococcal prevalence or infections were increasing in the study reported here, they had not reached alarming proportions. In fact the situation at the time when benzathine penicillin prophylaxis was instituted would be quite comparable to that encountered in a civilian population where benzathine-treated individuals would be subjected to less streptococcal exposure than is usually the case in military populations during streptococcal epidemics. Thus, one would expect a period of protection in a civilian population similar to that observed in this study.

One of the problems confronting responsible medical personnel is to determine when penicillin prophylaxis should be instituted in a recruit population. Actually, the problem narrows down to the ways and means of recognizing a streptococcal epidemic before it occurs. This is very difficult to do, even with bacteriological support. In the usual course of events, prophylaxis against streptococcal disease is instituted only when streptococcal isolation rates are elevated to some arbitrarily determined level; or when cases of scarlet fever and rheumatic fever begin to appear in the populations; or in the absence of these diseases, when infections that appear to be of streptococcal origin (pharyngeal and tonsillar exudate, high leukocyte counts, and large and tender cervical lymph nodes) are being observed frequently.[4] By the time it is determined that prophylaxis should be initiated, streptococci have been widely disseminated throughout the population and the groundwork already laid for the subsequent development of some cases of rheumatic fever. It was seen in this study that in spite of the fact that penicillin prophylaxis was instituted at what was thought an early stage of an impending epidemic, 33 cases of rheumatic fever developed. Thus, to prevent cases of rheumatic fever from occurring in a recruit population, it is almost

mandatory to institute penicillin prophylaxis before there is any laboratory or clinical evidence of streptococcal disease.

Because streptococcal disease occurs regularly in recruit training centers at some time during the winter and spring seasons, one solution to the problem would be routine, continuous, penicillin prophylaxis prior to the epidemic season. The principle behind this proposed method for the prevention of streptococcal disease is the same as that for justifying the present routine immunization schedule now employed by the military against typhoid, smallpox, diphtheria, and tetanus. For the past five years some form of penicillin prophylaxis has been employed against streptococcal disease at this station, and in the last two years benzathine penicillin has been administered during the epidemic season along with the routine immunizations. In both years the streptococcal epidemics have been halted; however, as was seen in this study, rheumatic fever was not entirely prevented. Thus, some continuous penicillin prophylactic program given annually just before and during the usual streptococcal season would seem warranted, in order to adequately control streptococcal diseases and their sequelae.

From the data presented in this study, it would seem mandatory, in formulating such a program, to take into consideration the possibility of maintaining a reservoir of epidemic streptococci in benzathine penicillin-treated companies later in their training period, if a single injection of benzathine penicillin is given early in training. This reservoir might, at the conclusion of prophylaxis, precipitate another outbreak of streptococcal disease. To prevent this from occurring, it might be desirable to administer the penicillin a little later in training as, for example, the beginning of the fourth week. This then would give protection almost to the end of training and yet if a man should acquire streptococci early in training, he eventually would be treated automatically, thus limiting any period of streptococcal parasitism sufficiently to prevent initial attacks of rheumatic fever. Such a program was instituted at this training center during the winter season 1956-1957, and only two cases of rheumatic fever and none of scarlet fever occurred among the recruit population undergoing prophylaxis. The details of this study will be the subject of a subsequent report. A similar program was conducted at another naval training center during the winter of 1956-1957, benzathine penicillin being administered in the third week of training.[11]

SUMMARY

During the winter of 1955-1956, approximately 26,000 Navy recruits at this training center underwent a penicillin prophylactic program against streptococcal disease. About one ha

received 157 mg (250,000 units) of buffered oral penicillin G twice daily for 10 days and once daily for an additional 30 days, while the other half received a single injection of 495 mg (600,000 units) of benzathine penicillin shortly after arrival at the training center. The oral preparation was employed in recruits "on-board" as of 21 January 1956, while benzathine penicillin was used in recruits entering training as of 18 January through 27 April 1956.

Although an overt streptococcal epidemic was prevented, 33 cases of rheumatic fever did occur in the recruit population as a result of streptococcal infections experienced prior to prophylaxis.

With the exception of one recruit, no positive cultures for group A streptococci were obtained in the benzathine penicillin-treated men until 28 or more days after injection, and only 0.4 per cent of men receiving the oral preparation showed positive cultures in the 40 day-oral prophylactic period.

In spite of this rather intensive penicillin prophylactic program, eradication of the epidemic type of streptococci from the recruit population was not accomplished, and a small streptococcal outbreak occurred near the conclusion of the study. Possible reasons for the failure to eradicate are discussed, and compensatory measures recommended.

Only 0.07 and 0.39 per cent of men receiving oral or benzathine penicillin, respectively, were hospitalized for hypersensitivity reactions. Reactions from benzathine penicillin were more severe than those from the oral preparation.

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HOW TO WHET THE READER'S APPETITE

"Next to the title, the most important section of a medical article is the summary. To the indexer, a properly written summary furnishes the necessary clues for cross-indexing the article. To the busy abstractor, it is a welcome digest of endless pages of printed words. To the assiduous physician, daily flooded with more literature than he can possibly peruse, it is the sample of a product which he must decide whether or not to purchase. But, unfortunately, too many authors fail to take advantage of this opportunity to sell their product by offering their prospective customers a truly representative sample, that is, a concentrated form of the real product. . . An informative summary should tell the reader as succinctly as possible the reason the paper was written and the salient points made in it. And it is just as important to know what not to include in the summary as what to include. For instance, no new facts should be introduced in the summary that have not already appeared in the body of the paper. Furthermore, there is no need to document statements made in the summary by citing references, as this should have been done in the body of the article. And, finally, reference should never be made in the summary to tabular or graphic material, as this also belongs in the body of the paper. . . . The summary should be a capsule version of the paper. A factual summary is one that will whet the appetite of the reader so that he will go back for a second helping."

—MICHAEL E. DeBAKEY, M. D.
CORA and WEBB MADING
in *Surgery*
pp. 946-947, Nov. 1957

Survival After Nephrectomy and Partial Nephrectomy for Bilateral Wilms's Tumors

JOHN L. FLANNERY, *Captain, MC, USN*

EMBRYONAL carcinosarcoma of the kidney (Wilms's tumor) is the most common malignant tumor of infancy and childhood. It is of embryonic origin, and as Sheach[1] pointed out may be multiple in one kidney or may involve both kidneys.

Surgical excision plus roentgen-ray irradiation may result in survival, and Rickham[2] recently reported the case of an infant who was progressing well 34 months after removal of simultaneously appearing, bilateral Wilms's tumors. An extensive review of the literature, however, fails to disclose a case comparable to the one herein described, in which there was a right nephrectomy at 14 months of age and a partial left nephrectomy at three years seven months of age for separate Wilms's tumors. Now, seven and one-half years after the first operation and five years after the second, the patient is enjoying good health without any evidence of metastasis or recurrence. Despite the absence of approximately two thirds of her normal renal mass, her growth and development has been normal.

CASE REPORT

First Hospitalization*

A 14-months-old female child was admitted to the U. S. Naval Hospital, Portsmouth, Va., on 18 October 1950 from the Ben Morreell Pediatric Clinic, Naval Air Station, Norfolk, Va., with admission diagnosis of Wilms's tumor. The patient had had frequent checkups, had received her immunizations, and was progressing normally. There had been no particular problems in her newborn or infantile period until 17 October 1950, when the mother noted a mass in the right side of the abdomen.

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*Pediatrician, Capt. J. L. Flannery, MC, USN; radiologist, Capt. G. C. Daughtridge, MC, USN (performed deep radiation therapy); urologist, Capt. A. C. Abernethy, MC, USN (performed right nephrectomy).

From U. S. Naval Hospital, Portsmouth, Va., and U. S. Naval Hospital, Great Lakes, Ill. Capt. Flannery is now Chief, Dependents Service, U. S. Naval Hospital, St. Albans, N. Y.

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The family history was noncontributory. Both the mother and father were living and well, and there were no siblings.

On physical examination, the abdomen appeared abnormally large, and on the right side a firm mass extended from the costal cage to the pelvic brim and medially to the midline. Other physical examination findings fitted a normal pattern for age.

Cystoscopy revealed no pathologic condition, but a retrograde pyelogram showed a greatly enlarged right kidney with the ureter extending across the midline (fig. 1). There was marked distortion of the calyces, with the superior calyces depressed inferolaterally and

Figure 1. Retrograde pyelogram showing grossly enlarged right kidney with ureter extending across the midline and part of pelvis at extreme right side of abdomen.

the inferior calyces pushed to the left and upward. The calyces and pelvis of the left kidney were within normal limits. Roentgenograms of the skeletal system and chest were negative, as were urinalyses and hematologic studies.

The urologic and surgical consultants were in agreement with the admission diagnosis of Wilms's tumor, and it was decided to perform

a nephrectomy, to be preceded and followed by x-ray therapy. The patient had six days of preoperative x-ray treatment totaling 1200 r in air, the daily therapy regimen being 200 kvp, 20 ma.-1.0 mm Al., 0.5 mm Cu.-50 cm dist., 10 × 15 - 200 r - 6' 2", alternating the anterior and posterior right abdominal fields. At operation on 31 October, the mass was roughly one half the original size. The kidney and tumor were removed through a transperitoneal approach. The pathologic diagnosis of the specimen, which has been corroborated by several pathologists, was Wilms's tumor of the right kidney showing radiation necrosis (fig. 2).

The patient was given a nine-day postoperative course of x-ray therapy totaling 1800 r in air, using the same radiation factors as in the preoperative course. Following the operation, she had an uneventful stay in the hospital, aside from a few mild bouts of radiation sickness, and was discharged home on 19 December.

From 19 December 1950 to March of 1953, the patient had frequent follow-up investigations for metastasis or recurrence. She enjoyed excellent health and progressed in a normal growth and development pattern, with no signs or symptoms relating to the previous pathologic condition in her right kidney.

Second Hospitalization*

On 23 March 1953, the patient was admitted to the U. S. Naval Hospital, Great Lakes, Ill., because of a mass in the left side of the abdomen. Two days previously she had complained of pain in the left flank and her mother discovered a mass there. There had been no premonitory symptoms, although two and one-half weeks prior to admission the patient had been examined for a febrile illness by a doctor who said that he felt nothing in the abdomen.

Physical examination revealed a well-developed, healthy appearing girl, with no evidence of weight loss. There was a right upper quadrant scar and an easily palpable mass that filled the left side of the abdomen from the rib cage to the iliac crest and medially to the umbilicus. There were no other physical findings of note.

The hemoglobin was 11.0 grams per 100 ml; the red blood cell count, 3,760,000 per μl; the white blood cell count, 10,950 per μl; and the blood urea nitrogen, 13.5 mg per 100 ml. Examination of the urine revealed rare white and red blood cells, but no albumin.

An intravenous pyelogram on 24 March (fig. 3) showed a fairly normal calyceal pattern in the left kidney. There was a mild hydronephrosis with upper ureteral dilatation and displacement medially. A large mass which could be nodes, tumor in the lower pole, or simply

*Pediatrician, Lt. P. S. Pierson, MC, USNR; radiologist, Capt. C. D. Burroughs, MC, USN (performed deep radiation therapy); urologist, Capt. M. W. Arnold, MC, USN (performed partial left nephrectomy).

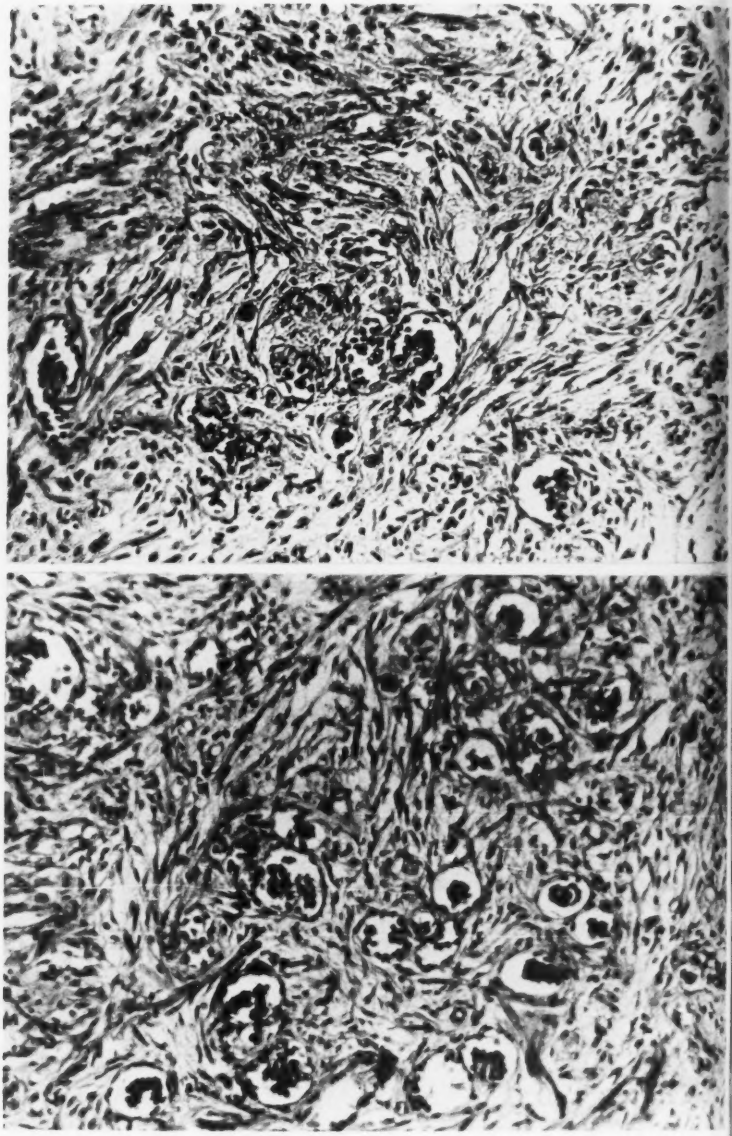

Figure 2. Photomicrographs of sections from right kidney with Wilms's tumor showing radiation necrosis.

Figure 3. Intravenous pyelogram showing medial displacement of ureter and mild hydronephrosis caused by large mass in area of lower pole of left kidney.

a hydronephrosis in the lower segment of a reduplicated kidney was present retroperitoneally, causing bowel and ureteral displacement. The kidney and related mass were freely mobile. Other x-ray and laboratory procedures were noncontributory. They presented no evidence of metastasis.

The most likely possibility appeared to be a tumor in the lowermost portion of the one remaining kidney, and it was decided to irradiate the tumor mass lightly to reduce its size, then remove it, and irradiate to a moderate extent postoperatively. Preoperatively the patient was given a total of 830 r in air, equally divided between left anterior and posterior midabdomen from a 220 kvp, 15 ma machine, with tube distance of 50 mm and filtration of 0.5 mm of copper and 1.0 mm of aluminum. With this therapy the blood pressure, blood count, and blood urea nitrogen remained normal.

At operation on 4 April the tumor had shrunk to the size of a lemon and was slightly cystic and friable. The operative report stated that

approximately the lower one third of the kidney was represented by a soft gelatinous, multicolored, multinodular tumor mass with hemorrhagic necrotic zones and a very thin, intact, veil-like capsule that was attached by thin adhesions to the surrounding tissues. When the adhesions were divided and the entire tumor mobilized, two small aberrant arteries and veins were seen to enter the lower pole of the kidney directly into the tumor mass. These were doubly ligated and divided.

The upper two thirds to three fourths of the kidney appeared normal in size, shape, color, and consistency, and a fairly sharp line of demarcation was present where this portion of the kidney merged with the tumor. A soft-shod rubber clamp was applied to the renal pedicle with just enough pressure to control bleeding, after which the kidney was resected. The incision extended circumferentially in a line about 1.7 cm proximal to the tumor demarcation in a normal-appearing portion of renal parenchyma, and transected the lowest minor calyx, which was closed with 0000 chromic catgut around a calyostomy tube, size 14-F. Irrigation of this tube with sterile saline solution showed a crystal-clear return flow. Several interlobar and arcuate arteries were identified by loosening the renal pedicle clamp. These were ligated. The renal parenchyma was then approximated, with a thin layer of fat (for hemostasis) between; and was mattress sutured, using plugs of perirenal fat to prevent the sutures from cutting into renal cortex. A second row of interrupted sutures were placed to effectively close the anterior and posterior parenchyma. The renal pedicle clamp was now removed and no bleeding was observed. One Penrose drain was placed in the depths of the wound, and along with the calyostomy tube was brought out through the posterior angle of the wound and secured. No surgical shock was evident at any time and the anesthesia was perfect.

The gross specimen sent for diagnosis consisted of a portion of kidney with attached tumor, which was well circumscribed, grayish brown, and about 4 cm in diameter. The portion of kidney was 1.5 by 3.0 by 3.5 cm. Microscopically (fig. 4), the tumor had a myxomatous, occasionally fibrosarcomatous stroma containing islands of deeply staining basophilic spindle-shaped nuclei or tubular structures lined by low cuboidal epithelium with hyperchromatic nuclei. There were occasional foci of hemorrhage and necrosis. The tumor had invaded the margins of the renal parenchymal tissue, and in the medullary region had obstructed collecting ducts, causing dilatation. There were some acute inflammatory cells within the stroma of the tumor. The diagnosis, as confirmed by several pathologists, was Wilms's tumor.

Postoperatively the patient did very well. Her blood pressure rose to 138/90 mm Hg on the second day after operation, but had returned to normal two days later. Blood chemistry determinations were remarkably normal. The blood urea nitrogen was 4.5 mg per 100 ml

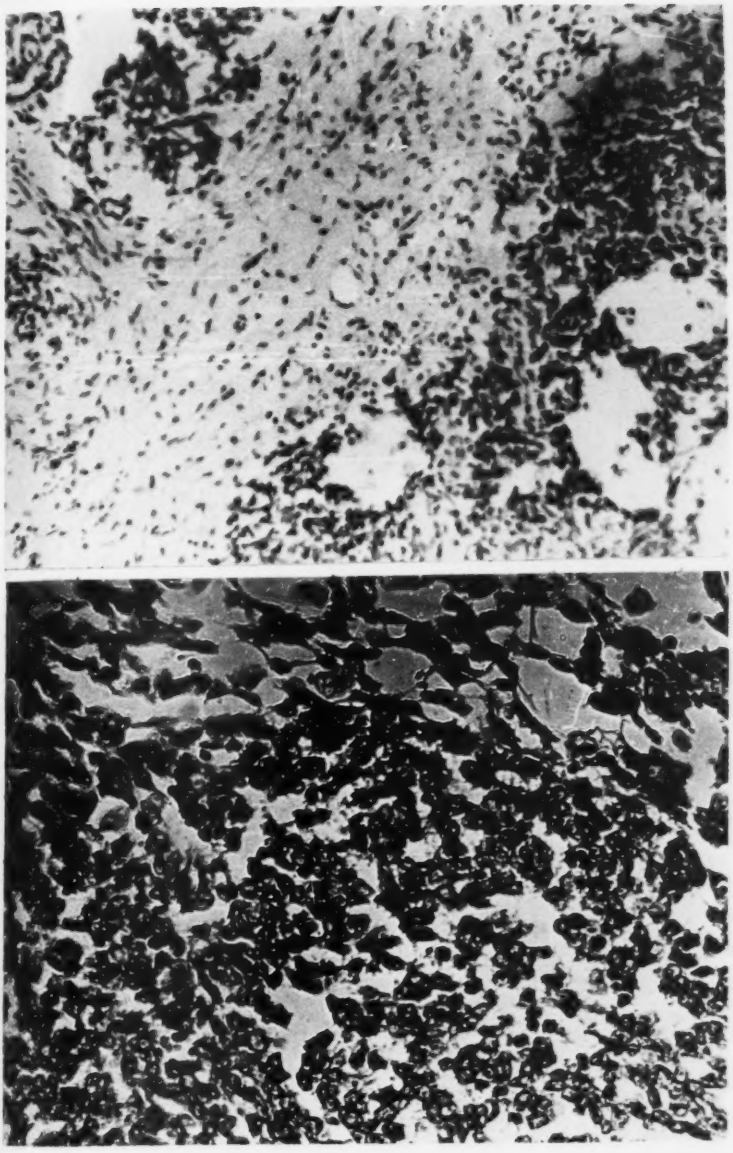

Figure 4. Photomicrographs of sections of specimen removed from left kidney, showing Wilms's tumor and areas of necrosis. (× 430)

four hours after operation and reached 17.5 six days later, but had returned to 9.5 the day prior to discharge. Creatinine, chlorides, hemoglobin, and red blood cell count remained essentially normal throughout. The 24-hour postoperative fluid intake was 1,280 ml (intravenous), and urinary output was 820 ml. The specific gravity of the urine varied during the first nine days from 1.010 to 1.020.

The patient was given a course of postoperative x-ray therapy, using the same radiation factors and regimen as for the preoperative course but totaling only 440 r in air.

The indwelling catheter was removed on the fourth postoperative day and the calyostomy tube on the eleventh day. The remainder of the hospital stay was without incident and the patient was discharged on 16 April.

From 16 April 1953 to the present, the patient has been followed closely. All results of repeated examinations and laboratory studies have been within normal limits or promptly returned to normal. Four years after the second operation, a checkup at Tripler U. S. Army Hospital, Honolulu, Hawaii, made by Captain L. Luke, MC, USA, showed blood urea nitrogen of 13.4 mg per 100 ml, a normal left excretory urogram with absence of the right kidney (fig. 5), and a normal

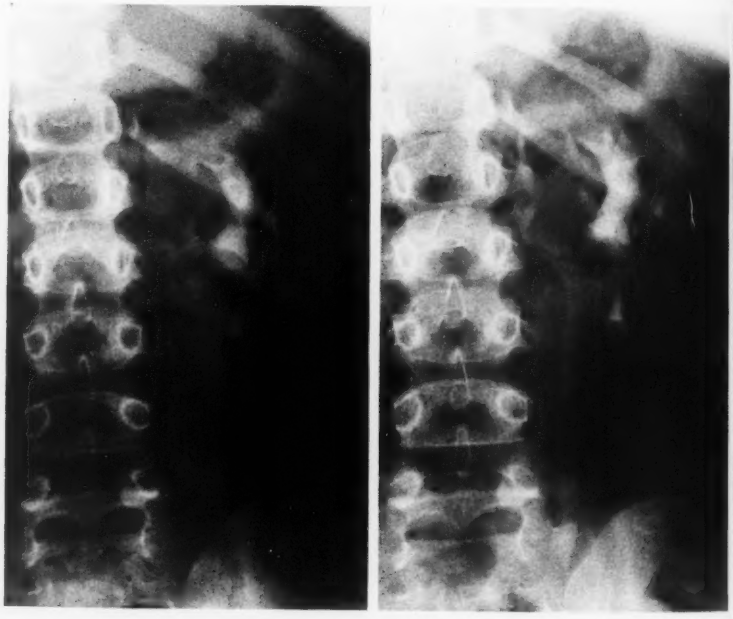

Figure 5. Excretory urogram of remaining portion of left kidney: left, after 5 minutes; right, after 10 minutes.

roentgenogram of the chest and long bones. The patient was completely asymptomatic and leading an active, normal life. A complete physical examination at the same hospital in November 1957 revealed that her condition had continued unchanged, with no evidence of metastasis or recurrence of the tumor. This was confirmed by report of 13 March 1958.

DISCUSSION

Embryonic mixed tumors were well evaluated as long ago as 1897 by Walker,[3] who pointed out that with early treatment there was at least some hope of survival. One question he raised still is not answered; namely, whether bilateral tumors are separate in origin or have a metastatic relationship.

In the present case, malignancy of the right kidney was treated by nephrectomy at 14 months of age. This is approximately the age at which Gross and Neuhauser[4] consider the best results are obtained. The patient showed no evidence of metastasis or recurrence for 30 months; then a tumor was discovered in the remaining left kidney. This was treated by resection, which Campbell[5] recommended in such a situation even though he considered that it offered only "an exceedingly long chance" of survival.

The passage of five years following the resection without any evidence of metastasis or recurrence makes it seem improbable that either will occur. Rusche[6] reported two cases of full-term, uneventful pregnancy several years after treatment for unilateral Wilms's tumor. This patient, who has only part of one kidney, has shown normal growth and development, presumably because of compensatory hypertrophy of the remaining portion of kidney, as described by Addis.[7] In her case, although an entirely new tumor could at some time arise from the remaining kidney tissue, such an unhappy outcome appears to be unlikely.

SUMMARY

The possibility of survival after surgical removal of bilateral Wilms's tumors accompanied by appropriate preoperative and postoperative deep x-ray therapy is illustrated by report of a case. Seven and one-half years after removal of the right kidney and five years after resection of the left, the patient continues in good health, with no evidence of metastasis or recurrence. In spite of removal of two thirds of her normal kidney mass, her pattern of growth and development apparently is unaltered.

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TEAMWORK IN WRITING

"Anyone developing new procedures or having new concepts should be willing to discuss and share them with others. No one should underestimate the power of an idea or the effectiveness of the pen. A discussion may be concerned with clinical or experimental subjects. For example, before a disease can be discussed, the normal findings should be given or shown, thus laying the basis for an understanding of the altered physiologic state. Anyone writing should recognize that research is the result of cooperation and team work. An ophthalmologist may need the assistance of the clinician, the histo-chemist, the physiologist, the pathologist and other specialists in medicine to aid him in his research. These work as a team, thus each may be better informed to the end that the patient may be better served. There are compensations from such united efforts as: (1) offering the opportunity for men in various specialties to better know each other and understand the language of their respective fields of interest; (2) through the publications of the results of the work, wider dissemination of the findings of research will be made possible. The writer must recognize that the subject may not only be of interest to those in his specialty but may stimulate the interest of those in related medical fields. His contribution is but a part of a larger sphere of scientific endeavor in which many may participate. This may be an ideal, but in actuality, often the most valuable findings have stemmed from the work of one individual who with a dynamic idea had a practical, workable plan of procedure in solving a problem."

—EDITORIAL
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Thyrotoxicosis With Thyrocardiac Crisis and Granulocytopenia

Following Therapy With Propylthiouracil

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VICTOR F. CORSIGLIA, Jr., *Lieutenant, MC, USNR*

THE TERM "thyrotoxic crisis" is now generally used to imply a fulminating increase in all signs and symptoms of thyrotoxicosis. Such a crisis is a dire medical emergency that is life-endangering. McArthur and associates[1] considered thyroid crisis not a complication of thyrotoxicosis but an intrinsic feature of the disease, a state being reached in which the patient is no longer capable of adjusting to the strain imposed by the hyperthyroidism. It is a multifaceted syndrome, and the symptomatology that develops depends on the relative vulnerability of body systems such as the central nervous system, the cardiorespiratory system, the gastrointestinal tract, and the hepatorenal or the adrenal-pituitary axis.

We have observed a patient with thyrotoxic crisis who was gravely ill and survived the critical period with therapy directed mainly at improving cardiorespiratory function. This case is best described as one of thyrocardiac crisis.

CASE REPORT

A 38-year-old Caucasian married woman was first seen in the emergency outpatient clinic of this hospital on 3 September 1956, complaining of tachycardia, palpitation, and irregularity of her heart beat. Examination revealed a completely irregular rhythm with a ventricular rate of 130 per minute. Her blood pressure was 170/80 mm Hg., and her thyroid gland was diffusely enlarged. An electrocardiogram demonstrated intermittent auricular fibrillation with a ventricular response of 170 per minute, alternating with sinus tachycardia at a rate of 140 per minute. The auricular fibrillation spontaneously subsided and the patient felt well. Protein-bound iodine was 20.5 μg per 100 ml. The patient failed to keep her appointment for evaluation in the medical clinic.

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On 14 February 1957 the patient again appeared at the emergency outpatient clinic and was admitted to the hospital. She stated that since September 1956 she had had short episodes of palpitation with a rapid, irregular heart beat, and that during the three days prior to her admission this condition had been continuous. She had noted moderate dyspnea and orthopnea. For the preceding 24 hours there had been nausea but no vomiting. She was employed as a school teacher and had worked the day of admission. She had noted nervousness, a gradual onset of difficulty in sleeping, increased appetite, and a decreased tolerance to heat. She perspired easily. There had been no weight loss, but rather a gradual 4-pound gain during the past month. Menstrual periods were regular, every 28 days, but scanty in flow, and lasting one to two days.

She had lived most of her life in Wisconsin. Seventeen years prior to admission she had a thyroglossal duct cyst excised without complications. She also had an appendectomy in 1954 and pneumonia at ages 8 and 16 years. She had one child, 12 years of age.

Physical Examination. The patient was well developed and well nourished, but was moderately nervous and apprehensive. Her temperature was 99.6° F, and respirations were 22 per minute. Her skin was warm and moist. Slight bilateral exophthalmos was present without other eye signs. A course tremor was noted. The thyroid gland was diffusely enlarged, approximately three times normal size, with a small, well-healed surgical scar over the cricoid area. The heart beat was irregular with a ventricular rate of 140 per minute. There was a systolic murmur over the apical area. Blood pressure was 180/90 mm Hg. A few moist rales were present in the lung bases. The liver and spleen were not palpable and there was no significant adenopathy.

Laboratory Studies. The white blood cell count was 7,500 per μl, with 55 per cent neutrophils, 40 per cent lymphocytes, and 5 per cent monocytes. Hemoglobin and hematocrit were normal. Urinalysis was negative. The serologic test for syphilis was negative. Total serum cholesterol was 130 mg per 100 ml, protein-bound iodine was 12.8 μg per 100 ml, and the basal metabolic rate was plus 60 per cent. An electrocardiogram on 14 February demonstrated auricular fibrillation (fig. 1). A roentgenogram of the chest on 15 February showed edema of the lower lung fields (fig. 2).

Figure 1. Auricular fibrillation evidenced in electrocardiogram made on 14 February 1957.

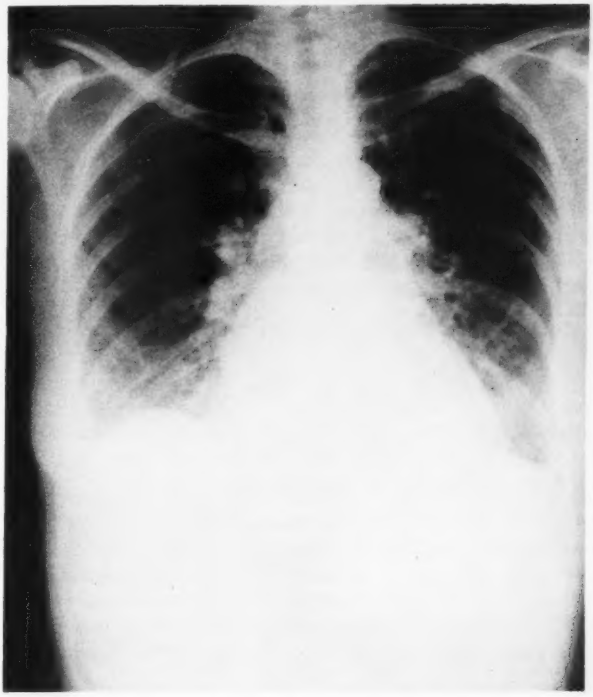

Figure 2. Edema of both lower lung fields shown in roentgenogram made on 15 February 1957.

Course in Hospital. On admission therapy consisted of bed rest, sedation with Nembutal, a high caloric diet, and 200 mg of propylthiouracil every eight hours. Starting four hours after the first propylthiouracil was administered, 0.6 ml of a saturated solution of potassium iodide was given orally three times daily.

During the first 24 hours of hospitalization, the patient appeared to be doing well on this regimen, having no respiratory difficulty, eating well, and not appearing to be particularly nervous or toxic. During the second night she became restless and apprehensive, and could not sleep. These were interpreted as toxic symptoms and she was sedated heavily with barbiturates and morphine sulfate, with some diminution of symptoms.

Early the next morning the patient became acutely dyspneic, orthopneic, cyanotic, and semicomatose, with thrashing movements of the extremities. Moist rales were present throughout both lung fields. The heart beat was totally irregular, at 150 per minute, and the heart sounds were faint. Blood pressure was 140/90 mm Hg., and temperature

was 100.2° F. There was slight pitting edema of the ankles, and the neck veins were distended.

Therapy consisted of immediate positive pressure oxygen, digitalization with 1.6 mg of Cedilanid (brand of lanatoside C) intravenously, 2 ml of Thiomerin Sodium (brand of mercaptomerin sodium) intramuscularly, placing the patient in a sitting position in an armchair, and applying cold towels to her chest. The response was dramatic. The cyanosis cleared, and after one hour the heart sounds were forceful and the rate slowed to 125 per minute. Soon after, the patient complained of being hungry and was given fruit juices and high-protein, high-carbohydrate malted milk as desired.

The improvement was continuous. Diuresis occurred during the first 24 hours, with the resultant loss of 7 pounds of weight. The patient was kept in the armchair for six hours and then returned to bed. Propylthiouracil was increased to 300 mg every six hours, and the potassium iodide was discontinued. She was maintained on 0.5 mg digitalin daily, high caloric diet with vitamin supplements, and sedation with small doses of barbiturates.

The signs of thyrotoxicosis began to regress rapidly on 25 February. The basal metabolic rate was plus 30 per cent. A roentgenogram of the chest was normal. The thyroid gland had enlarged moderately under therapy. A few lymph nodes in the left cervical area were palpable, and there was a transient episode of urticaria on both lower extremities.

During the next several days the patient felt well except for occasional "chilly" sensations, and during this time she had a low-grade fever ranging from 99° to 101°F.

On 1 March bilateral cervical lymphadenopathy was noted, but the temperature was normal. Weekly white blood cell and differential counts had remained essentially as on admission. On 1 March the white blood count was 9,400 per μl with 41 per cent neutrophils, 35 per cent lymphocytes, 8 per cent monocytes, 7 per cent eosinophils, and 2 per cent basophils. Hemoglobin was 13.6 grams per 100 ml. Hematocrit was 44 ml per 100 ml.

On 5 March the patient was given a small test dose of quinidine sulfate for hypersensitivity, and on the following day normal sinus rhythm was attained with a total dose of 800 mg of quinidine given orally in a two-hour period. Following conversion, the electrocardiographic findings were normal.

The patient remained essentially asymptomatic, although there was a persistence of the bilateral cervical lymphadenopathy. On 8 March her temperature spiked to 101°F and her right submaxillary gland became swollen and tender, but she continued to feel well. On this day the white blood cells numbered 10,700 per μl with 3 per cent band forms, 63 per cent lymphocytes, 30 per cent monocytes, and 4 per cent basophils.

The propylthiouracil was discontinued, and 1,200,000 units prophylactic procaine penicillin daily and 2 grams of Terramycin (brand of oxytetracycline) daily were started. There was a complete absence of neutrophils for three days, although the peripheral smear did contain some eosinophils and basophils. On 11 March there were a few juvenile neutrophils (metamyelocytes). By 15 March the white blood cell count and differential had returned to 5,800 per μl with 50 per cent neutrophils, 44 per cent lymphocytes, and 6 per cent monocytes.

During the period of granulocytopenia, the patient was relatively asymptomatic. By 15 March symptoms of thyrotoxicosis began to reappear, the pulse rate had increased from 90 to 110, and tremor was present again. On 18 March the patient was transferred to the U. S. Naval Hospital, San Diego, Calif., where she was treated with iodine 131. She has been followed periodically in this clinic, and as of 26 October 1957, is euthyroid, clinically well, and without evidence of cardiovascular disease.

DISCUSSION

This patient had had thyrotoxicosis for several months. She was admitted to this hospital without previous treatment, and although she had typical signs and symptoms of thyrotoxicosis, her major complaints and physical findings were related to the cardiorespiratory systems. At that time it was indeterminate as to whether she had coexisting thyrotoxicosis and cardiac disease, or primary thyrotoxicosis with secondary cardiac signs and symptoms.

Therapy initially was directed toward the thyrotoxicosis, and consisted of bed rest, high caloric diet, sedation, and antithyroid drugs. Although the patient was bordering on congestive heart failure, it appeared that treatment of her thyroid disease would correct her cardiac difficulty. Twenty-four hours following admission, she became restless and anxious. The examiner interpreted this as being caused by increased thyroid toxicity, and the patient was heavily sedated, but without any particular benefit. It is well documented that a patient with thyrotoxicosis has an increased oxygen demand.[2] In this case the anxiety, apprehensiveness, and restlessness were due primarily to congestive heart failure and cerebral anoxia secondary to thyrotoxicosis. This condition has been frequently termed thyroid storm. If immediate steps are not taken to correct the heart failure and oxygen lack, the results will be disastrous.

The therapy in this case at the time of the critical period was directed primarily toward cardiac failure and anoxic anoxia. The response was dramatic and the patient required no further sedation for a period of 12 hours and then only small doses of barbiturates. While it is understood that there are many facets to the treatment of a patient with thyrotoxicosis in a critical

state, steroids and intravenous dextrose did not seem to be indicated following the patient's response to the above therapy.

Propylthiouracil was increased to 1,200 mg per day in order to bring the patient to an euthyroid state as soon as possible. Large doses of propylthiouracil have been used by Bartels and Kohn[3] in patients such as ours with good results and no particular increase in side reactions. While the improvement in our patient was rapid with the large dose of propylthiouracil, the patient did develop granulocytopenia. McGavack and Chevalley[4] reported that there is an increased incidence of granulocytopenia (from 0.1 to 0.3 per cent) with doses larger than 150 mg daily. The iodine was discontinued because the definitive treatment decided upon in this case was iodine 131.

SUMMARY

A patient with thyrotoxicosis developed signs and symptoms that would be interpreted as thyroid storm. The primary cause of the anxiety, apprehensiveness, and restlessness were cardiac failure and cerebral anoxic anoxia, as demonstrated by the fact that she responded to specific therapy directed toward the heart failure and anoxia. She approached the euthyroid state very rapidly on large doses of propylthiouracil, but developed granulocytopenia, which subsided on discontinuance of the drug. She subsequently was treated with iodine 131. At the present time, she is euthyroid, clinically well, and without evidence of heart disease. Such cases of thyrotoxicosis and impending cardiac failure should be treated as any other case of congestive failure, while the primary thyroid disease is being brought under control.

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Mycetoma Pedis

A Case Report Emphasizing Radiographic Changes

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MYCETOMA, or maduromycosis, is a chronic granulomatous disease which usually affects the foot but that also has been reported in other parts of the lower extremity, scrotum, trunk, and upper extremity. The disease, though not common, should be of interest to the military services because of its chronicity and because the only hope for cure and rehabilitation lies in its early diagnosis.

While mycetoma is usually thought of as a disease associated with the tropics, it also is found in temperate zones and is worldwide in distribution. The first case in the United States was reported by Hyde, Senn, and Bishop[1] in 1896. The incidence in North America is relatively low, but it probably is higher than indicated in the medical literature or in public health reports. According to Quinland and Chenault,[2] a total of 57 cases had been reported to 1950, 19 of these being in the decade 1941-1950. Burns, Moss, and Brueck[3] noted that the number of reported cases seemed to follow the curve of investigation of the subject, and suggested that during periods of low incidence many cases were unrecognized, being classified as chronic osteomyelitis of the foot. This is not unusual, and patients certainly have been separated from the military service with unrecognized mycetomas.[2]

Mycetoma is caused by a large variety of fungi belonging to many species and genera, and by many actinomycetaceae. The greatest number of documented cases in North America were caused by actinomyces or nocardia. The pathologic changes and the clinical course, however, are the same regardless of the etiologic agent, and laboratory studies are necessary to differentiate one infection from another. It was thought originally that specific organisms produced specific colored granules, but it has been shown that a single organism in the same patient can produce granules of different colors.[4] The granules, which may be white to yellow, red or black, are conglomerations of the organisms.

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In the maduromycoses, granules of true fungi are found which contain large, segmented mycelium with well-defined walls and, often, chlamydospores. The granules in actinomycoses contain fine, nonsegmented filaments with poorly defined walls and no chlamydospores. Even when this distinction has been made, further classification may assume some importance, for good results have been reported with sulfanilamide in cases in which the causative organism was nocardia. The difficulty lies in growing the organism on culture media. Green, Bolton, and Woolsey[5] have pointed out that growing the organism really requires special effort.

The incubation period in this disease is unknown, but it may be weeks or months. The inoculation is believed to be a product of trauma, although it is not always possible to elicit this history. There are cases reported which were associated with trauma that did not result in a visible break in the skin surface, and it is likely that a similar situation prevails in those cases in which no trauma is reported.[3]

The greatest number of cases of mycetoma involve the foot, and this is particularly true in areas where shoes are not worn. There are cases with foot involvement in persons who normally are shod, however, so that the wearing of shoes by military personnel does not preclude their becoming infected if they come in contact with the pathologic organism.

The clinical course is slowly progressive over a period of years. There may be periods of remission, but spontaneous cure is rare if it occurs at all. The organisms are aerobic but seem capable of extracting sufficient oxygen from the tissues in which they are located, and the initial symptoms may not appear for a considerable period after healing of the original injury.

The early symptoms are pain and tenderness followed by the development of a hard, deep-seated, nodular lesion accompanied by swelling. The swelling extends peripherally, and additional nodules develop. The nodules soften and rupture, with discharge of pus containing the characteristic granules. Drainage may continue for a few days and be followed by healing-over of the sinus, but the healing is generally superficial overlying superficial or deep-seated abscess cavities. Various phases of the process are present at the same time, and there is marked fibrosis as the disease progresses over the years. No tissue is spared. Fascial planes offer no barrier, and bone is involved as well. The end result is a swollen, distorted, globose appendage. The toes are separated and misdirected. This is the result of an increase in the soft parts due to fibrous proliferation with resultant lymphatic obstruction, and of fibrous contractures. Pain is present but not excruciating, and the major difficulty is one of impairment of locomotion.

There is a paucity of information in the literature with respect to the radiographic changes in mycetoma pedis. Many of the standard texts contain no mention of the disease. Brailsford[6] wrote: "Radiographs show marked osteoporosis associated with multiple rounded areas of cancellous destruction which represent foci of infection. The lesions, which may be found in any bones of the foot, may become confluent; they are perhaps most prominent when they involve the metatarsals." Shanks and Kerley[7] were even more brief, and stated that there are no characteristic features. They quoted Benassi and Fiaschi[8] as finding the radiographic changes to be those of osteoperiostitis, with predominating new bone formation. These are the only authors to report this finding. Carroll[9] summarized the changes by stating that the principal findings are cystic destruction of bone, with little surrounding bone reaction, and irregular thinning of the shafts of the metatarsals and phalanges. Carter[10] reported that the bones are diffusely destroyed and barely visible on the film. He further pointed out that when single lesions are presented, there may be little or nothing to suggest mycosis, but that where foci are multiple and varied, a tentative diagnosis may be profitable. Another point mentioned is a striking absence of surrounding bone reaction and sclerosis.

Thirteen case reports in the literature[2,3,5,9,11–16] were reviewed in an attempt to determine if the mycotic bone lesions were purely destructive or if any cases showed the osteoperiostitis and predominant new bone formation of Benassi and Fiaschi. Of the 13 cases, the bone changes are not mentioned in 1; in 1, no bone changes were present; in 1, the changes described were entirely sclerotic; in 2, there was mixed destruction and proliferation; and in 8, the only changes were those of destruction. In all cases there appears to have been demineralization, which apparently was secondary to disuse and to associated overlying soft tissue inflammatory reaction. Those cases with destructive changes include both simple loss of bone substance, particularly in cancellous bone, and an apparently classical punched-out appearance to the bone, particularly in the shafts of the metatarsals and phalanges. This is illustrated in figure 1. The multiple, round areas of bone destruction represent the sinus tracts, and in the smaller bones may show some expansion. If these sinus tracts involve just the bone margin, a half-moon effect is produced. The radiographs reproduce the clinically apparent spreading of the phalanges and metatarsals by increased volume of soft tissue. The normal margination and planes of cleavage in the soft tissues are lost. The surface nodularity also is evident on films. In a far-advanced case, the destruction may result in a lacelike pattern of the remaining bone.

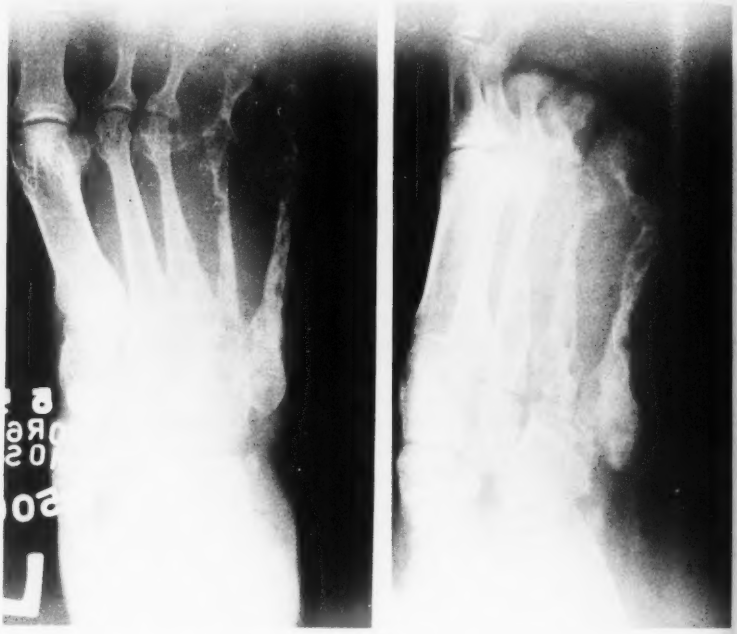

Figure 1. Classical radiographic appearance with generalized demineralization and punched-out areas of bone destruction. The punched-out areas represent sinus tracts through bone.

CASE REPORT

A 26-year-old Panamanian woman sustained an injury to the right ankle in 1942. The initial injury was slow to heal. About one year following the injury she was given surgical treatment elsewhere. The exact nature of this treatment to the right ankle is not known. During the next seven years she had intermittent pain in the leg and sores were present about the ankle. The symptoms had been worse during the six months preceding her initial admission to this hospital in April 1950.

The records indicate that she had received some form of dispensary care during the period 1948-1950, but the physical findings at that time are not known. She was referred to the radiology department of this hospital in July 1948 with a clinical diagnosis of "chronic leg ulcer." At that time the roentgenograms showed a marked periosteal proliferation of the distal right fibula (fig. 2). The tibia appeared normal and the ankle joint was intact. The changes were interpreted as compatible with chronic stasis and chronic leg ulcer. A second roentgenographic examination 13 months later showed, in addition to the periostitis, an area of increased density and of rarefaction in the medullary portion of

the fibula (fig. 3). The changes were interpreted as a chronic osteomyelitis.

Figure 2 (July 1948). First radiographic changes reported in present case. Note the periosteal proliferation along distal fibular shaft.

On admission to this hospital in April 1950, the complaints were pain and deformity in the right leg and foot. On physical examination, the right ankle was fixed in equinus and there was resistance to flexion and extension. There were skin changes over both malleoli consisting of depigmentation, scar formation, thinning, and loss of hair. There was a tender, fluctuant area over the lateral malleolus. Draining sinuses developed over the ankle. *Micrococcus pyogenes* var. *aureus*, sensitive to streptomycin sulfate, was cultured from the discharge. The sinuses became quiescent on antibiotic therapy. Roentgenograms at this time showed considerable change over the outpatient examination in August 1949. An irregular radio-density was reported in the os calcis, and it was stated that the changes indicated a chronic osteomyelitis of the os

calcis and distal fibula. After six weeks the patient was returned to dispensary care.

Figure 3 (August 1949). Progressive changes in 13 months consisting of area of increased density and rarefaction in medullary portion of fibula. Findings interpreted as chronic osteomyelitis.

The second hospitalization covered the period 27 June 1951 to 16 July 1951, and the clinical picture was a duplication of that seen on the first admission, except for evidence of progression. Progressive roentgenographic changes are shown in figure 4. These were described at some length, with the conclusion that they represented far-advanced osteomyelitis of undetermined cause with an associated aseptic necrosis of the os calcis.

The final hospitalization was from November 1953 to January 1954. The chief complaint was pain and drainage in the right foot, which had greatly increased in size. The skin was reddened, considerable tenderness was present, and there were about two dozen draining sinuses over the dorsum of the foot. No motion was present in the ankle. There was an enlarged, tender, femoral node. The patient had been treated with both antibiotics and sulfanilamide with no improvement.

Figure 4 (July 1951). Progression of lesion in approximately three years to involve os calcis. Note that process is predominently proliferative but evidence of sinus tracts is present.

The first films seen by me were dated 13 November 1953. They showed the old periosteal reaction along the right distal fibular shaft. There was marked irregular demineralization of the distal ends of both bones of the leg and all bones of the foot. A fairly large area of bone and joint destruction was present in the mid-tarsal area, and scattered, smaller defects were noted within the several bones of the foot. There was also some irregular condensation of bone, most marked in the os calcis. Swelling of the soft tissues was noted. A diagnosis of Madura foot was made (figs. 5 and 6).

Biopsy for culture resulted in identification of nocardia as the offending organism. Amputation of the right leg in the proximal third was

Figure 5 and 6 (November 1953). Final radiographic appearance 5 years after original examination and 11 years following original injury.

carried out on 8 December 1953. The inguinal node enlargement regressed and was probably a manifestation of secondary bacterial infection. The patient was last seen in March 1954. The amputation stump was well healed and there was no evidence of recurrence.

DISCUSSION

This case is recorded because it presents so many features that are characteristic of mycetoma pedis, and because the progressive radiographic changes, which certainly do not fall into the generally accepted mycotic pattern, are so well documented. There was a definite history of trauma with slow healing of the initial wound, followed by a chronic, protracted course, marked by exacerbations and remissions. Deformity was present, as were pain and tenderness. The condition was inaccurately diagnosed as chronic osteomyelitis on several occasions over a period of years. The end result was a painful, useless appendage that required amputation.

This is not offered as a criticism of the various clinicians who saw the case at one time or another. Mycetoma is a fairly unusual condition that first must be considered before diagnosis can be made, and even then a positive diagnosis is often difficult to establish. Nor is any criticism of the radiologists implied, for the changes in this case did not fit the classic mold, even when the advanced stages were reached. The presentation is meant simply as a reminder that mycetoma should be kept in mind. Had the correct diagnosis been considered early, efforts to prove it might have been fruitful, and perhaps the final result might have been avoided or postponed. Several cases, particularly those in which nocardia has been identified as the infecting organism, have been reported as showing good results on treatment with sulfanilamide. The results have not been uniform, however, and it is unlikely that a favorable result should have been expected in this case once the diagnosis was established. The disease process was too well established and too extensive.

In this specific case, surgical excision, rather than amputation, probably would not have been possible even in 1948 when the radiographic changes were confined to the fibula. The decision would have depended on the extent of the soft tissue involvement at that time. There are, however, other cases where the infection may be localized sufficiently to permit surgical excision. Gottlieb[15] reported a cure in a patient with a five-year history of a mycetoma in which the changes were confined to the plantar aspect of the foot and which permitted treatment by resection rather than by amputation. The patient whose foot is shown in figure 1 may have fallen into this category at an earlier stage when the involvement was limited to the lateral aspect of the foot. He was, unfortunately, lost to follow-up.

The radiographic changes in this case do not fit the classical pattern as shown in figure 1. However, in the advanced stages they permitted an accurate diagnosis, and there were changes in the os calcis in 1951 which might have suggested mycetoma. It would appear from many of the cases reported in the literature that mycotic infections are purely destructive in their reaction on bone, and that the productive bone reaction occasionally seen is due to the stimulation of secondary invaders. In this case, *Micrococcus pyogenes* var. *aureus* was cultured from the pus on several attempts. Thus, the radiologist must be aware of the possibility of obscuration of the true nature of the disease by complicating factors.

SUMMARY

A discussion of the clinical and radiographic features of mycetoma pedis has been presented, with a case report that illustrates the problems and difficulty of diagnosis. While no pathognomonic radiographic changes have been definitely established, certain features, when present, should suggest the diagnosis. The disease, though rare, is of world-wide distribution and of importance to the military services. It probably is more prevalent than recorded cases would indicate. Because of its low incidence it is not considered in the differential diagnosis of bone lesions as often as it should be, and it is believed that inclusion of this condition by the radiologist among the differentials offered may alert the clinician early enough in the course of the disease to permit earlier and more successful therapeutic measures.

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THE FATHER OF MODERN CHEMISTRY

"The year is 1790, the scene is Paris. The thunder of the Revolution shakes the earth. Yet in the quiet and calm of his laboratory, Antoine Laurent Lavoisier is putting a great question to nature. He has been told that when substances burn they lose a mysterious material called phlogiston. Lavoisier did not believe it. He asked, 'How do you know that?' 'If phlogiston exists,' said Lavoisier, 'I shall get it and weigh it on the balance and compute it by mathematics. If I cannot weigh it or compute it by mathematics it does not exist.' And thus with this spirit of wholesome inquiry he showed that burning was not the dephlogistination of matter but a combining with oxygen. 'And then what about breathing?' inquired Lavoisier. He described the oxygenation of blood in the lungs and developed the biological chemistry of the pulmonary circulation described by Servetus.

"But Lavoisier was an aristocrat and the Revolution rabble was in the saddle. He was snatched abruptly from his experiments and tried before the revolutionary tribunal. Robespierre drew his finger around his neck and declared, 'The republic hath no need of savants.' On May 2, 1794, third in a line of 28, Lavoisier rode in the tumbril over the cobbled streets of Paris to the Place de la Concorde. The guillotine fell. Lagrange very trenchantly commented, 'It took but a minute to sever that head; France will be a century in producing another like it.' This statement was prophetic, because France did not produce another citizen like Lavoisier until the advent of Louis Pasteur. With the simplicity to wonder he has been fittingly called the 'father of modern chemistry.'"

—JOHN C. KRANTZ, Jr.
in *Connecticut State Medical Journal*
p. 828, Sept. 1957

PRESIDENT EISENHOWER IS MADE HONORARY FELLOW OF AMERICAN COLLEGE OF SURGEONS

In a White House ceremony on 6 February, President Eisenhower was made an honorary fellow of the American College of Surgeons. He is shown above, wearing the hood of the College. Left to right are Major General Howard McC. Snyder, USA (Ret.), White House physician; Dr. Brian Blades, Professor of Surgery, George Washington University School of Medicine; Major General Leonard D. Heaton, MC, USA, Commanding General, Walter Reed Army Medical Center; Dr. John H. Lyons, Washington, D. C.; the President; Dr. I. S. Ravdin, Professor of Surgery, University of Pennsylvania School of Medicine, and Chairman of the Board of Regents of the College, who read the citation the President is holding; Dr. Frank B. Berry, Assistant Secretary of Defense (Health and Medical); and Robert Cutler, special assistant to the President for National Security Affairs and president of the board of trustees of Peter Bent Brigham Hospital, Boston.

ADM. KENNEY NAMED ASSISTANT BUMED CHIEF, SUCCEEDED AT BETHESDA BY CAPTAIN KREUZ

Rear Admiral Edward C. Kenney, MC, USN, recently promoted to flag rank, has reported for duty as Assistant Chief for Personnel and Professional Operations, Bureau of Medicine and Surgery, Department of the Navy. A combat veteran of World War II, Admiral Kenney was awarded the Navy Cross for extraordinary heroism while serving as senior medical officer of the U. S. S. *Boise*, and the Bronze Star Medal with combat "V" for meritorious service while participating in landings on Guam, Leyte and Lingayan Gulf.

Rear Admiral Thomas F. Cooper, MC, USN, right, Commanding Officer of the National Naval Medical Center, congratulates Rear Admiral Kenney on his promotion.

Captain Kreuz.

Captain Frank P. Kreuz, MC, USN, has succeeded Admiral Kenney as Commanding Officer of the U. S. Naval Hospital, Bethesda, Md. A diplomate of the American Board of Orthopedics since 1948, he has served as chief of the orthopedics services at the U. S. Naval Hospitals in Philadelphia and Bethesda. During World War II he was senior medical officer on the staff of the commander, Battle Force Pacific, aboard the U. S. S. *Washington*, and was awarded the Bronze Star. His most recent assignment was Commanding Officer of the U. S. Naval Hospital, Guam.

BRIG. GEN. M. S. WHITE INSTALLED AS PRESIDENT OF AERO MEDICAL ASSOCIATION

Brigadier General M. S. White, USAF (MC), was installed as president of the Aero Medical Association at the conclusion of the Society's 29th annual meeting in Washington, D. C., last month.

Captain Ashton Graybiel, MC, USN, Director of Research at the U. S. Naval School of Aviation Medicine, Pensacola, Fla., outgoing president of the Association, directed the activities of the three-day meeting on March 24, 25, and 26, which attracted nearly 1,500 aeromedical scientists from thirty countries. More than 100 speakers in the extensive scientific program presented research advances directly related to the biologic aspects of flight, and particularly the conquest of outer space.

General White.

The Association's Theodore C. Lyster Award for outstanding achievement in the field of aviation space medicine was won by Dr. Hubertus Strughold, Medical Research Advisor to the Commandant of the Air Force School of Aviation Medicine. Dr. Siegfried J. Gerathewohl was the recipient of the Arnold D. Tuttle Award. Brigadier General Victor A. Bymes and Colonel Harry G. Moseley, USAF (MC), received the Eric Liljencrantz and Raymond F. Longacre Awards, respectively.

Captain Oran W. Chenault, MC, USN, and Colonel Benjamin A. Strickland, Jr., USAF (MC), were elected members of the Executive Council for a three-year term. Military physicians advanced to the grade of fellow include Rear Admiral Winfred P. Dana, MC, USN (Ret.); Captains Norman L. Barr, William M. Snowden, and Carl E. Wilbur, MC, USN; Colonel Charles H. Roadman, USAF (MC); Major David G. Simons, USAF (MC); and Dr. Hubertus Strughold. Dr. Howard T. Karsner, Research Advisor to the Surgeon General of the Navy, was elected an honorary fellow.

A flight surgeon for more than 20 years, General White is Director of Medical Staffing and Education for the Air Force Surgeon General. In 1940 he made the first electrocardiograph recordings and the complete scientific study of heart action of pilots during high-altitude flight. This study led to the development of technics for the recording of biological functions which are now widely used in the investigation of human factors in flight. In 1945 he was a member of the Air Force group which pioneered the first scheduled round-the-world military air transport flights in six days.

GEN. KENNEBECK, AIR FORCE DENTAL CHIEF, RECEIVES LEGION OF MERIT ON RETIREMENT

Major General Marvin E. Kennebeck, Assistant for Dental Services, Office of the Air Force Surgeon General, was awarded the Legion of Merit in retirement ceremonies on 31 January 1958. Brigadier General James S. Cathroe is the new Assistant for Dental Services.

Major General Dan C. Ogle, Air Force Surgeon General, presents Legion of Merit to Major General Kennebeck.

General Kennebeck, an early advocate of the fluoridation of water supplies at Air Force bases, was appointed Assistant for Dental Services in June 1952. He initiated the Air Force Preventive Dentistry Program which has contributed immeasurably to the high health standards of the Air Force, and introduced the panoramic dental x-ray machine and the use of chrome cobalt alloy to replace gold in dental work. During General Kennebeck's Washington assignment, dental-officer and post-graduate training was more than doubled to afford the highest type of professional training to Air Force dental officers. General Kennebeck was born in Carroll, Iowa, and received the degree of doctor of dental surgery from the University of Iowa in June 1924. He entered on active duty on 9 September 1924 as assistant dental surgeon at Walter Reed Army Hospital. He is former president of the Armed Forces Commission of the *Federation Dentaire Internationale* and past vice-president of the American Dental Association.

WHO CELEBRATES TENTH ANNIVERSARY

On April 7, the traditional date of World Health Day, the World Health Organization observed its tenth anniversary.

Doctor Candau

"This day provides an excellent opportunity to review the strides made towards our goal 'of the highest possible level of health' during the past decade of national and international effort," said Doctor M. G. Candau, Rio de Janeiro, Brazil, director-general of WHO. "There have been great scientific advances during this period and this new knowledge is being rapidly applied where it is needed. In the last 10 years the flow and exchange of scientific information and practical experience have perhaps been greater than ever before. More scientists and health workers than ever before have gone from country to country to learn, to teach and to demonstrate."

Russian Medical Translations Available

The Pergamon Institute, a nonprofit foundation, was recently formed in Washington, D. C., and London for the purpose of making available to English-speaking scientists, doctors, and engineers, from United Nations countries, the results of scientific, technological, and medical research and development in the Soviet Union and other countries in the Russian orbit. More than 100 scientists of international standing have given their support to this project and will supervise the affairs of the Institute. Dr. Detlev W. Bronk and Sir Robert Robinson, O. M., F. R. S., are joint presidents of the Institute's board of governors.

The Institute publishes, in English, the following Russian medical journals: *Biophysics; Sechenov Physiological Journal; Problems of Virology; Problems of Hematology and Blood Transfusion; Journal of Microbiology, Epidemiology and Immunobiology;* and *Problems of Oncology.* These periodicals, and other selected translations, including microcards and microfilms, are available to individual physicians and scientific societies.

The Institute plans to hold a symposium during the summer of 1958, either in Washington or London. Additional information can be obtained from the Pergamon Institute, 122 East 55th Street, New York 22, N. Y.

Medical Writing Award Announced

The editors of *Modern Medical Monographs,* a quarterly publication, announce an award for the best unpublished manuscript for a short book on a clinical subject in the field of internal medicine. The purpose of this award, which will be known as the Modern Medical Monograph Award, is to stimulate young physicians to communicate their work in the classical form of the monograph and to achieve high standards of medical writing. The winner of this competition will receive $500. In addition, the winning monograph, if found suitable, will be published as a book in the series *Modern Medical Monographs.*

The entries will be judged for style and clarity of expression by a committee of the American Medical Writers' Association and for clinical interest and scientific value by the editors and advisory board of *Modern Medical Monographs.* The award will be governed by the following rules:

1. The author, or authors, must be a graduate physician, less than 40 years of age. Single authorship is preferred, but two coauthors will be acceptable. The name of the medical school from which the author graduated and his date of graduation should be stated.

2. Manuscripts should be submitted in duplicate (original and one copy) by registered mail, postmarked no later than October 1, 1958, to Richard H. Orr, M. D., 37 East 67th St., New York 21, New York.

3. The manuscript, including the bibliography, must consist of between 115 and 200 double-spaced typewritten pages with ample margins and not more than 40 illustrations (figures or photographs). For each illustration used, the allowable upper limit of typewritten manuscript pages should be reduced by one.

4. Fishbein's book, "Medical Writing" (third edition), should be followed in preparation of the manuscript, use of abbreviations, and bibliographic form.

ARMY ENDS SHIPMENT OF BOOKS TO KOREA

The American-Korean Foundation and the United States Army Medical Service have announced the discontinuance of their joint project of shipping medical books contributed by individual physicians, medical schools, hospitals, and state and local medical societies to Korea. Books should *not* be sent to the Sharpe General Depot in California, as in the past, because facilities no longer exist for packing and transshipping to Korea.

In making this announcement, Howard A. Rusk, M. D., Chairman, the American-Korean Foundation, said, "The response of physicians and medical groups throughout the country to our appeal for books for Korean medical schools has been so generous that such further contributions are no longer needed."

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OFFICERS CERTIFIED BY SPECIALTY BOARDS

Supplementary Listing

The following regular Medical and Dental Corps officers have been certified by the boards indicated since the listings published in previous issues of this *Journal*, according to information from the Offices of the Surgeons General of the military medical services:

American Board of Pediatrics

Edwin A. Meeks, Maj., USA

American Board of Psychiatry and Neurology

Psychiatry

Martin B. Giffen, Lt. Col., USAF
Boaz Harris, Maj., USA
Dermott A. P. Smith, Maj., USA

American Board of Orthopaedic Surgery

Frederick R. Hook, Jr., Maj., USAF

American Board of Dermatology and Syphilology

Charles H. Wells, Maj., USA

American Board of Radiology

Wallace W. Bednarz, Capt., USAF

American Board of Pathology

John G. Webster, Capt., USAF

American Board of Surgery

Benjamin R. Baker, Maj., USAF
James A. Bulen, Maj., USAF
Dean M. Ring, Maj., USAF
Evan W. Schear, Lt. Col., USAF
Jacob F. Schirmer, Lt. Col., USA
John H. Sharp, Lt. Col., USA

American Board of Anesthesiology

Herman R. Hansen, Maj., USA

American Board of Prosthodontics

Clare W. Sauser, Lt. Col., USA

DEATH

NOVAK, Louis (n), Chief Medical Service Warrant Officer, USN, of Philadelphia, Pa.; stationed at the U. S. Marine Corps Recruit Depot, Parris Island, S. C.; served in the United States Navy in an enlisted status from 9 April 1931 until 15 January 1944; appointed Pharmacist in the United States Navy 16 January 1944; died 17 February 1958, age 44, at the U. S. Naval Hospital, Beaufort, S. C., of carcinoma of the lung.

EDITORIAL

WHITE HOUSE DOCTORS

One of the feature articles in *MD Medical Newsmagazine,* which made its debut a year ago, is entitled "White House Worriers."[1] It struck your Observer as a rather apt title for a dissertation on Presidential physicians.

Any physician responsible for the health of a prominent individual is constantly aware that his ministrations are under close scrutiny. This is especially true when the patient happens to be the President of the United States. . . .

The century and a half during which physicians have served Presidents covers nearly the whole medical history of the United States, "from the blood-letting of Washington to the electrocardiography of Eisenhower." Illustrative of the professional relationships and medical progress are sketches of selected Presidential physicians who have watched over a President's health in war and peace. These are: James Craik (1730-1814), Philip Syng Physick (1768-1837), Robert King Stone (1822-1872), Benjamin Fordyce Barker (1818-1891), Ross T. McIntire (1889—), and Howard McCrum Snyder (1881—). Drs. Physick, Stone, Barker, McIntire and Snyder were or are members of the Medical Society of the District of Columbia.

Like Dr. Snyder, the present White House Physician, Dr. Craik had been closely associated with the President he served before he took office. He was with General Washington in the war against the French and later the British.

By modern standards, Dr. Craik's methods were crude. MD states he "knew no other remedy than blood letting, gargling with vinegar and sage tea, and the application of Spanish Fly (Cantharis, the 'blister bug') to the throat." He treated the President for a variety of respiratory conditions, carbuncles, inflammation of the eyes, and recurrent malaria. His consultants were Drs. Elisha Dick and Gustave Brown. They knew little more than he did.

Dr. Physick practiced during the same period. It appears that he had a recalcitrant patient in President Andrew Jackson: "Wild, and hot tempered, the soldier-lawyer rode roughshod over medical advice, placed his faith in lead acetate for practically any ailment." He was one of a legion of patients before and since who knew better than his physician what was wrong with him. However, he had a wholesome respect for Dr. Physick because of the high regard in which he was held professionally. Nevertheless, he protested: "I can do anything you think proper, except give up coffee and tobacco."

Reprinted with permission from *Medical Annals of the District of Columbia* 27: 85-86, Feb. 1958.

President Jackson suffered from chronic pleurisy due to a bullet lodged in or around the pericardium received in a duel in 1806. Dr. Physick's chief remedy for pleurisy was cupping. He also prescribed freely "heroic doses of lead acetate and calomel" to prevent the President's self-treatment.

Dr. Stone was President Abraham Lincoln's personal physician. Lincoln usually ignored his doctor's prescription of shorter work hours and longer bed rest. He suffered from hypochondria, then attributed to defective digestive functions. This contributed to melancholy, which "dripped from the tall gaunt man."

Chronic constipation, a sluggish circulation, a poorly functioning liver, an apparent deviation of the left eye, and a suspected tendency to tuberculosis were conditions for which President Lincoln was treated. A remedy prescribed by one of Dr. Stone's predecessors for the President's general condition was "blue pills" (mercury mass).

President Ulysses S. Grant sought out Dr. Barker as his physician. Theirs was a satisfying personal relationship. He treated the President for malignancy of the throat. The treatment consisted of the "application of a solution of muriate of cocaine (4 to 12 per cent) two or three times a day. Potassium permanganate and brewer's yeast were used in gargles, iodoform was applied to the diseased tissue by insufflation.". . .

The diagnostic procedures followed and therapy prescribed by Dr. Snyder and his associates in the treatment of President Dwight D. Eisenhower, as compared with those of his predecessors, illustrate the phenomenal progress of medical science. Time, too, has wrought great changes with respect to the secrecy which in the past surrounded the afflictions of Chief Magistrates. No longer is there any attempt to conceal even the elemental physiologic processes which relate to the President's health.

One may question the good taste or even the necessity for these revelations, but where the President's physician is concerned, frankness relieves him of the burden imposed by secrecy. It offers him an opportunity to disclose who the consultants are, their professional standing, and their views with respect to the state of the President's health. In his position, he cannot afford mistakes, for they will not be overlooked nor excused. So he surrounds himself with the ablest consultants to confirm, modify or reject his findings.

All in all, for the White House doctor this is a far better day. He has at his command diagnostic aids and therapy undreamed of by his predecessors. As a result, he should worry less and sleep better nights.

REFERENCE

1. White House Worriers. *MD Medical Newsmagazine* 1: 20-26, Feb. 1957.

A MESSAGE FROM THE A. M. A.

Since 1952, the Council on National Defense of the American Medical Association has conducted an opinion survey among physicians being released from active military service. The questionnaire used in the survey is primarily designed to obtain pertinent data based on the physician's observations and opinions while in the Armed Forces, concerning the utilization of physicians and the medical staffing conditions in the uniformed services. The questionnaire also is designed to elicit comments and suggestions as to further improvement of military medical services as well as ways and means whereby organized medicine can be of greater assistance to military physicians.

This report covers the period 1 January 1956 to 31 December 1956. During that period the Council sent out 2,519 questionnaire forms. Of these, 1,600 were completed and returned, representing a 64 per cent response.

Age Distribution of Responding Physicians. About 40 per cent (644) of the physicians replying were in the 30-34 year age group. In the 25-29 year age group, there were 584 (about 37 per cent), while in the 35-39 year age group there were 284 (11 per cent) of those responding.

Date of Graduation From Medical School. More than half of the responding physicians were graduated from medical school subsequent to 1949; the second largest group, about 36 per cent, graduated during the period 1945-1949. None failed to indicate the year of graduation from medical school.

Years of Residency Training. The largest group (410 physicians, or about 26 per cent of those replying to this question) had no residency training, while the second largest group (308 physicians, or 19 per cent) had but one year of residency training at the time of entrance on active duty. There were 223 (14 per cent) who had two years; 277 (17 per cent) who had three years; and 159 (10 per cent) who had four years of residency training.

Occupation at Time of Entering Service. The largest groups of physicians who served in the Army and Navy (24 and 27 per cent respectively) were engaged in general practice at time of entrance on active military duty, while the largest group in the Air Force (36 per cent) was in internship. The summary report for the year 1955[1] showed that the largest groups in the Army and Air Force were engaged in general practice, while the largest group in the Navy was in residency training prior to active military service.

From the Council on National Defense of the American Medical Association. The views and opinions expressed are not necessarily those of the Department of Defense. —*Editor*

Number of Physicians Holding Board Certificates. Of the 293 persons responding to the question, 131 holding specialty board certificates were in the Army, 125 were in the Navy, and 37 were in the Air Force. The specialties covered over 19 different fields of which the largest was internal medicine, the second largest was surgery, and the third largest was pediatrics. In the previous report, for the year 1955, internal medicine was first, followed by pediatrics and surgery. By branch of service, a total of 22 per cent of those responding in the Army, 20 per cent of those in the Navy, and 10 per cent of those in the Air Force had specialty board certificates.

Government Medical Education Received. A total of 533 of the 1,600 physicians responding stated that they had received assistance in their medical education from the Federal Government, while 1,067 indicated they had received no Government assistance. The largest single group receiving Government assistance was under the Army Specialized Training Program. The next two largest groups were under the Navy V-12 Program and the GI Program. Of the responding physicians, 64 per cent of those who served in the Army, 67.3 per cent of those in the Navy, and 70 per cent of those in the Air Force received no Government assistance.

Training Received While in Service. There were 895 of the physicians responding who received military medical training while on active duty in the Army, Navy, or Air Force. The Medical Field Service School accounted for 632, the largest number, while 156, the second largest group, received training at the School of Aviation Medicine. In the Army group, about 82 per cent received the Basic Course training of the Medical Field Service School, as did nearly 8 per cent of those in the Navy and 24 per cent of those in the Air Force.

Physicians' Evaluation of Military Medical Training. The great majority of physicians filling out the questionnaire thought that all important features of military medical training had been satisfactorily covered. For the Army, 82 per cent were satisfied with the training, while 67 per cent of those in the Navy and 85 per cent of those in the Air Force were satisfied. A small percentage indicated that the training was unsatisfactory, but gave no specific reasons. Others stated reasons why they considered their tour of service unsatisfactory. Most of these physicians in the Army and Air Force reported insufficient training in military customs, administration, and regulations as an unsatisfactory aspect of military medical training, while most Navy physicians reported insufficient basic orientation and indoctrination.

Physicians' Evaluation of Assignment. The vast majority of responding physicians stated that their longest and next longest

assignments were almost completely, or partially but satisfactorily, in line with their training and experience. With respect to the longest assignment, 80 per cent of the Army physicians, 73 per cent of the Navy, and 87 per cent of the Air Force physicians replying were of the opinion that the assignment was almost completely, or partially but satisfactorily, in line with training and experience. In regard to the next longest assignment, the percentages were 72, 75, and 78 per cent, respectively, for the favorable opinions of Army, Navy, and Air Force physicians. Consistent with this evaluation, the vast majority also expressed satisfaction with the same assignments. In answer to both questions, a greater portion of the Air Force physicians responded favorably than did Army or Navy medical officers.

Types of Patients Treated. One of the questions was designed to determine the percentage of time devoted by physicians to military personnel, dependents of military personnel, and administrative duties, both at domestic and overseas stations. On assignments in the United States nearly 47 per cent of the reporting physicians devoted one half or more of their time to the treatment of military personnel, while nearly 39 per cent devoted one half or more of their time to the treatment of dependents of military personnel. At overseas stations nearly 30 per cent of the physicians replying devoted one half or more of their time to military personnel and 12 per cent devoted one half or more of their time to dependents of military personnel.

Types of Nonmilitary Medical Care Provided. The question that was designed to determine the types of medical duties most frequently performed for nonmilitary persons elicited the information that in all three of the armed services outpatient care ranked first at domestic and overseas stations. In the Army, general medical and hospital care was second in the United States, while pediatrics was second at overseas stations. In the Navy, pediatrics was second at domestic installations, while general medical and hospital care was second overseas. Obstetrics and gynecology was second for Air Force physicians in the United States and pediatrics was second at overseas bases.

Medical Care of Dependents by Civilian Medical Personnel. With respect to service in the United States, the great majority of responding physicians were of the opinion that all medical care of nonmilitary persons could have been adequately performed by civilian military personnel. In the three military services, 816 of 1,316 physicians (62 per cent) so responded. In regard to overseas service, however, only 127 of 495 physicians (26 per cent) were of that opinion.

REFERENCE

1. Message from the A. M. A. *U. S. Armed Forces M. J.* 8: 449-451, Mar. 1957.

CORRESPONDENCE

Nerve Gas Poisoning

To the Editor:—I have been interested in the paper which appeared on page 1726 of the December 1957 number, by Oberst et al., on the use of the Batrow neuromuscular stimulator in GB-poisoned animals. I am very puzzled, however, that nowhere in the article was there any discussion as to why this form of stimulator, as well as the Sarnoff stimulator, could not possibly work.

In both curare poisoning and in poisoning by such cholinesterase depressants as GB nerve gas, the pathology is a transmission from motor nerve to muscle deficit at the myoneural junction. If the normal nerve impulse is unable to get across and contact the muscle, it is absurd to expect that the nerve impulse produced by an electric current could work. Both of the stimulators mentioned in this article are effective in stimulating the motor nerve through their faradic properties, i. e., a rapid reversal of electric current in the case of the Sarnoff stimulator 60 times a second, and in the case of the Batrow stimulator, a short pulse of only 7 microseconds in duration that is introduced 60 times a second. Denervated muscle by means of chemical block at the end plate can only respond electrically to a direct current type of stimulator, which has so far not been designed, as far as I know. There is ample evidence in the literature and in the experience of clinicians that in polyneuritis, curare poisoning, myasthenia gravis, and in nerve gas poisoning, the muscle will not respond to stimulation of the motor nerve. This is not true in drowning, poliomyelitis, or paralysis of breathing due to increased intracranial pressure or damage to the medulla and spinal cord. Both of these stimulators were designed and recommended for this kind of respiratory difficulty, where the peripheral part of the motor nerve is equipped with a normally transmitting motor end plate.

I think it is exceedingly important that readers of the *Journal* understand clearly the reason why electrophrenic respiration can never work in motor end plate disturbances, or instances where the peripheral part of the motor nerve is not functioning, and that they were never expected or intended to be effective here. This paper in no way vitiates the success of these stimulators in the types of respiratory difficulty mentioned above, where the motor end plate is intact.

ROBERT S. SCHWAB, *Commander, MC, USNR (Ret.)*
Massachusetts General Hospital
Boston, Mass.

Doctor Schwab's letter was referred to Doctor Oberst, who made the following comment after consulting with his co-workers:

To the Editor:—We agree with Dr. Schwab that when the neuromuscular junction is degenerated or blocked, electro-stimulation of the nerve cannot cause muscular contraction. Our experiments described in our article show that under controlled conditions we were unable to induce artificial respiration in GB-poisoned dogs and monkeys with the Batrow neuromuscular stimulator. The equipment did produce unselected muscular contractions, but this did not move sufficient air for survival of the animals. Doubtless this type of stimulation cannot set up the reciprocal innervation required for respiration to be effective.

FRED W. OBERST, *Ph. D.*
U. S. Army Chemical Warfare Laboratories
Army Chemical Center, Md.

Asian Influenza

To the Editor:—We have read with interest the article by L. S. Greene and T. A. Hair, Jr., on "Clinical Experience With 682 Cases of Asian Influenza," which appeared on pages 385 to 390 of the March 1958 issue of the *U. S. Armed Forces Medical Journal.* There now is available certain additional information concerning this outbreak that may be of value to your readers and serve to place the article in true perspective.

The final Epidemiological Report submitted to the Bureau of Medicine and Surgery, Department of the Navy, indicated that a total of 1,891 cases occurred at the Naval Air Station, Memphis, Tenn., during the epidemic, with an attack rate of 16.7 per cent. Those cases having severe prostration or fever of 100° F or over at the time first seen were transferred to the hospital. The clinical characteristics discussed in this article, therefore, represent the findings in approximately 35 per cent of the total cases, with the remainder presumably having had a milder disease free of significant complications. While not detracting from the value of the article to physicians working in hospitals, this points up the quite different impression of a disease to be gained by a physician cognizant of the total series of cases. The distribution of fever, frequency of complications, and other characteristics found in a hospital series of patients thus cannot be considered as characteristic of the disease.

The reports further indicated that most immunization was not given until after the beginning of the epidemic. Medical Department personnel

who received the intracutaneous immunization in advance of other personnel on the station had a much lower attack rate, despite their heavy exposure.

In the absence of controls, this does not provide unequivocal evidence, but is suggestive of the fact that the vaccine may have decreased the frequency of acquiring the disease, even if not modifying it once acquired. However, the general impression of medical officers in the Dispensary of the Air Station was that the vaccine had little effectiveness despite the above finding in Medical Department personnel.

HOWARD K. SESSIONS, *Captain, MC, USN*
Director, Preventive Medicine Division

JOHN R. SEAL, *Captain, MC, USN*
Head, Communicable Disease Branch

Bureau of Medicine and Surgery,
Department of the Navy, Washington, D. C.

Medical Education Week, April 20-26

The third annual Medical Education Week will be observed 20-26 April throughout the United States to focus attention on, and inform the public of the ever-increasing contribution of medicine to American life, and of the basic significance of medical education. The general objectives of this observation are to develop public understanding of the progress, aims, and problems of medical education in the hope of stimulating more adequate financial support. The committee of organizations sponsoring Medical Education Week include Lowell T. Coggeshall, M. D., president, Association of American Medical Colleges; David B. Allman, M. D., president, American Medical Association; Louis H. Bauer, M. D., president, American Medical Education Foundation; S. Sloan Colt, president, National Fund for Education; Robert Rakel, president, Student American Medical Association; and Mrs. Paul C. Craig, president, Women's Auxiliary to the American Medical Association.

Reviews of Recent Books

THE BASES OF TREATMENT, by *Neuton S. Stern*, A. B., M. D., and *Thomas N. Stern*, M. D. 176 pages. Charles C Thomas, Publisher, Springfield, Ill., 1957. Price $4.75.

This book is the outgrowth of a course in therapeutics given by the authors at the University of Tennessee College of Medicine. The subject is approached from the point of view of presenting the principle upon which all therapy is based, rather than outlining in detail specific treatment of various disease states. Thus, the book should serve as a useful guide to the medical student and practitioner alike for many years, even though specific therapeutic agents may change.

The publication of such a volume at this time appears particularly appropriate because it stresses the general symptomatic care of the patient which is so often overlooked in this era of specific remedial agents. It is one which the physician could well have in his library to pick up and read from time to time with a view to refreshening himself on the general principles which should be kept in mind in administering to the sick. —*GEORGE M. POWELL, Col., MC, USA*

SURGICAL TECHNIQUE and Principles of Operative Surgery, by *A. V. Partipilo*, M. D., F. A. C. S. Foreword by *Alton Ochsner*, M. D., F. A. C. S. 6th edition. 966 pages; 1,235 illustrations on 719 figures, 4 in color. Lea & Febiger, Philadelphia, Pa., 1957. Price $20.

Surgeons acquainted with previous editions of this work will anticipate and discover a still greater contribution to surgical technic in the sixth edition. In 38 completely new chapters and the 43 revised chapters, the reader will find detailed technics of every significant surgical procedure he will ever employ.

Pragmatic discussions of fluid therapy, transfusions, anesthesiology, radioisotopes, radiation therapy, and suturing are presented prior to the chapter on operative technics. In discussion of a given procedure, ample consideration is accorded the indications for surgery, the risk, and the pre- and postoperative management. Of particular merit are the 1,235 illustrative line drawings of operative procedures, anatomic principles, and physiologic considerations. Reasons are presented, step by step, for the operative maneuvers. In a review of basic surgical information and operative principles, students, residents, and practicing surgeons will find valuable questionnaires concluding each chapter invaluable. The objectives of this stimulating book have been commendably achieved by the author, namely, the review of (1) pertinent surgical anatomy, (2) essential physiology, (3) correlated pathology, and (4) fundamental clinical aspects of each subject. There is timely emphasis on the importance of diagnosis and valid indications for a given procedure.

This is truly a functional book covering all important aspects of surgery of the neck, the chest, the heart and great vessels, the abdomen,

and related specialties; its extreme usefulness derives from the point-by-point description of a sound and tested procedure exactly as it is performed by a great teacher. —*JAMES B. ANDERSON, Lt. Col., USAF (MC)*

THE INFANTILE CEREBRAL PALSIES, by *Eirene Collis*, et al. 100 pages. Charles C Thomas, Publisher, Springfield, Ill., 1957. Price $3.

In exactly 100 pages this book covers an amazingly wide range of topics concerning cerebral palsy, ranging from the fascinating story of William Little's classical descriptions of the disease to a detailed plan for the organization of cerebral palsy services.

The authors are members of the Little Committee, formed 100 years after Little's original description of this entity for the purpose of studying the clinical problems of diagnosis, prognosis, management, and the administrative problems involved in training medical and other personnel for work in the field of cerebral palsy. They describe a dynamic educative process in which the day-to-day work is carried out by the combined efforts of the child and his mother, the cerebral palsy service giving the required advice and encouragement.

Separate chapters are devoted to the different forms of cerebral palsy, and each chapter includes a typical case history, with the details of management appropriate to it and the manner in which advice is given to the mother. The *raison d'etre* of this small, well-written book is to offer a practical guide for those concerned with the panoply of problems caused by cerebral palsy. —*THOMAS E. CONE, Jr., Capt., MC, USN*

THE CLINICAL APPLICATION OF ANTIBIOTICS, by *M. E. Florey*, M. D. Volume III, Chloramphenicol and the Tetracyclines. 393 pages; illustrated. Oxford University Press, New York, N. Y., 1957. Price $19.50.

This volume, a continuation of the author's earlier work, *Clinical Application of Antibiotics—Penicillin*, published in 1952, evaluates critically the data on which the present use of antibiotics was founded. Chloramphenicol and the tetracyclines (chlortetracycline or aureomycin, oxytetracycline or terramycin, and tetracycline or achromycin) are covered in this volume. Each is dealt with separately and evaluated in three different categories, with a chapter devoted to each. The first chapter includes the general consideration, such as origin and properties, antibacterial action, complications of therapy, results of clinical trials, and administration. The middle chapter deals with the treatment of disease due to a specific organism, such as rickettsial diseases, viral diseases, diseases caused by bacteria, venereal diseases, and tropical and miscellaneous diseases. The last chapter for each drug covers the treatment of diseases considered by system, age group, or sex. This includes diseases of the heart, nervous system, lungs and bronchi, infections within the abdomen, obstetric and gynecologic conditions, infections in infancy, genitourinary infections, otolaryngological infections, infections of the skin, infections of the eye, and bacteremia.

The author has covered in detail each of the drugs under consideration by an extensive review of the literature. The effectiveness and routes of administration and complications are discussed. The results of clinical trials are summarized for each drug, showing the specific infections which are consistently responsive, those which have variable response or no response, and also those conditions in which the substance was ineffective in a trial of treatment. This volume is considered excellent for those interested in a review of the literature for each of these individual drugs and an evaluation of their usefulness and effectiveness in the treatment of patients. For the average physician, however, it is too detailed to be read completely, but would make an excellent source of reference for any individual disease or infection where treatment with one of these antibiotics is being considered. —*DOSS O. LYNN, Col., MC, USA*

CLINICAL ORTHODONTICS, A Guide to the Sectional Method, by *Bercu Fischer,* D. D. S. 478 pages; 1,332 illustrations on 354 figures. W. B. Saunders Co., Philadelphia, Pa., 1957. Price $17.

The author tactfully relates his experiences in the practice of orthodontics, adhering to his postgraduate training in the aspects of Angle's teachings, which was, basically, a classification of diagnosis, en masse tooth movement in treatment, and the sanctity of a full complement of teeth. Dissatisfaction with orthodontic results obtained and individual barriers encountered caused the author to search for the reasons and a solution. This lead to personal clinical research and a break from Angle's concepts.

The author clearly describes his reasons for divergence from the impact of Angle's concepts upon clinical practice. He outlines, in detail, clinical data and conclusions to substantiate a new approach in orthodontic treatment based on the individual. Clinical research dictated that diagnosis be made after complete consideration of the individual. Heredity, asymmetries, dentofacial complex, tissue tolerance, arch approximation, compensatory adjustment, and functional adaptation are factors of human individuality that are specifically its own. Individual variability becomes the basis of diagnosis. A diagnosis, based on individual variables, is then treated sectionally, with or without tooth extractions, establishing the corrected denture as close as possible to the patient's individual functional pattern, maximum stability, and to dental and facial esthetics.

The author's methods of diagnosis and recording are described with the use of numerous illustrations, drawings and photographs. A chapter devoted to appliances and technics also is amply illustrated and diagrammed. Another chapter contains an atlas of case reports which analyze clinical procedures in sectional orthodontic treatment.

Although dealing with a controversial subject, this book is well written and ably presented as a new approach to the basic principles

in the management of patterns of malocclusion. Its value lies in the fact that the practices described are those used in the author's own clinical practice and is intended as a practical guide.

—*GEORGE S. MOORE, Col., USAF (DC)*

THE DERMATOLOGIST'S HANDBOOK, by *Ashton L. Welsh,* M. S., M. D. American Lecture Series, Publication No. 293, A Monograph in The Bannerstone Division of American Lectures in Dermatology, edited by *Arthur C. Curtis,* M. D. 427 pages. Charles C Thomas, Publisher, Springfield, Ill., 1957. Price $15.

The author of this handbook attempts "to organize into a rational systemic classification for purposes of instruction and ready reference, that large number of topical and internal therapeutic agents concerning which a dermatologist must have knowledge." The book is divided into three sections on topical therapy, internal therapy, and reference data. In the topical therapy section, a review of some of the more useful "standard" dermatologic prescriptions is presented. It also contains a valuable and relatively complete review of topical pharmaceutical specialties. The author fails to make his internal therapy section broadly inclusive because of the very reasons which motivated his concentration on this section, the ever-increasing pharmaceutical armamentarium and the vastness of the subject. In the section on reference data there are useful charts and some practical therapeutic points. On the whole, the author succeeds in presenting a relatively complete and useful ready reference book for the busy dermatologist.

—*SAMUEL L. MOSCHELLA, Comdr., MC, USN*

QUANTITATIVE PHARMACEUTICAL CHEMISTRY, by *Glenn L. Jenkins,* Ph. D.; *John E. Christian,* Ph. D.; and *George P. Hager,* Ph. D. 5th edition. 552 pages; illustrated. The Blakiston Division, McGraw-Hill Book Co., Inc., New York, N. Y., 1957. Price $8.50.

This book is a new edition of one of the finest teaching texts in pharmaceutical chemistry. It furnishes students of pharmacy with a systematic course covering the quantitative chemical and physical methods of *The Pharmacopeia of the United States of America* and *The National Formulary,* classifies the official procedures according to type of analysis, and presents applicable nonofficial methods which are widely used in pharmaceutical chemistry. The authors have revised the text to conform with the revised official methods given in USP XV and National Formulary X. Although this text is designed for the student of pharmacy it will serve as an excellent reference source to all those engaged in drug analysis.—*ROY L. MUNDY, Capt., MSC, USA*

INTRODUCTION TO ANESTHESIA, The Principles of Safe Practice, by *Robert D. Dripps,* M. D.; *James E. Eckenhoff,* M. D.; and *Leroy D. Vandam,* M. D. 266 pages; illustrated. W. B. Saunders Co., Philadelphia, Pa., 1957. Price $4.50.

This small volume is rich with integrated facts. The authors touch on all aspects of anesthesia but particularly emphasize the pharmacology and physiology as related to anesthesia. The vast amount of material

is organized into five general headings of the preanesthetic period, the day of anesthesia, during operation, the postoperative period, and special topics. Under the latter, cardiac resuscitation, pediatric anesthesia, anesthesia for the ambulatory patient, obstetric anesthesia, management of narcotic poisoning, and inhalation therapy are included. This book would be a valuable source of information for residents who can discuss its contents with their teachers. It would help the busy clinical anesthesiologist organize much of the knowledge he has acquired piecemeal over the years. It is short on technics of anesthesia and, therefore, is not meant for the novice who tries to practice anesthesia without other help.—*DANIEL M. PINO, Capt., MC, USN*

ORTHODONTICS: Principles and Prevention (Companion Volume to Orthodontics: Practice and Technics), by *J. A. Salzmann*, D. D. S., F. A. P. H. A. 381 pages; 262 illustrations and 26 tables. J. B. Lippincott Co., Philadelphia, Pa., 1957. Price $13. ORTHODONTICS: Practice and Technics (Companion Volume to Orthodontics: Principles and Prevention), by *J. A. Salzmann*, D. D. S., F. A. P. H. A. 497 pages; 471 illustrations and 34 tables. J. B. Lippincott Co., Philadelphia, Pa., 1957. Price $20. (These two volumes are available in a slip case for $33 for the set.)

These companion texts were divided into two separate volumes for the convenience of the student, general dentist, and the orthodontist.

Orthodontics: Principles and Prevention is intended primarily for the student and the practitioner seeking fundamentals of orthodontics rather than for the specialist interested in advanced orthodontic technics. The introductory chapters consider orthodontics and preventive orthodontics in relation to the general practice of dentistry and public health programs. The succeeding eight chapters present the latest concepts of physical growth and development of the human body, including assessment of growth and development, bone growth, development and postnatal growth of the head and skull, and the development of the dentition and the occlusion of the teeth. The remaining three chapters describe anomalies, postnatal factors in malocclusion, and the prevention and treatment of incipient malocclusion. The text is written in an easy-to-read style and the well-chosen illustrations, charts and tables are reproduced in an excellent manner and should prove particularly worthwhile to both the student and the practitioner.

Orthodontics: Practice and Technics. The thirteen chapters in the book may be grouped under four major headings: etiology, diagnosis, treatment planning, and mechanotherapy. The use of the carpal index, cephalometrics analysis, and many of the related medical and dental phases of a complete examination are presented. In "Differential Diagnosis and Treatment Planning" the author describes the clinical manifestations of malocclusion in the deciduous, mixed, and permanent dentitions, indications and contraindications for the extraction of dental units, and the age of the patient in relation to diagnosis and treatment of dentofacial anomalies. Various technics in the use of fixed and re-

movable appliances for the correction of malocclusion are presented. The quality of paper, the printing style, and the reproductions are excellent. This book should be invaluable for advanced students and dentists interested in orthodontics.—*GEORGE H. PARROT, Lt. Col., DC, USA*

CORTISONE IN DENTISTRY, by *Lyon P. Strean,* M. Sc., Ph. D., D. D. S., F. A. P. H. A. 178 pages; 57 illustrations. Dental Items of Interest Publishing Co., Inc., Brooklyn, N. Y., 1957. Price $5.95.

The author of this small volume discusses the physiology of the adrenal cortex and its relationship with the anterior pituitary, including the chemistry and biochemistry of cortisone, hydrocortisone, corticosterone, and ACTH. He emphasizes the antirheumatic and anti-inflammatory properties of these substances and their effects on metabolism. The uses of the adrenal cortical hormones have been well established and this section of the book enables the dental practitioner and dental student not only to become acquainted with their use in systemic diseases, but gives them an excellent background for their application in many oral diseases.

The need for such a book has been evident for many years, and it is a revelation to read of the many applications of these "stress" hormones in oral diseases. It is well written in a clear, concise, and easily readable style. Illustrations, tables, and graphs are clear and pertinent. An adequate bibliography for further reference is contained at the end of each chapter, and a selected list of dental references on cortisone is included. This book should be in all dental libraries and is a necessity for the practitioner of dentistry.

—*THEODORE E. FISCHER, Col., USAF (DC)*

INTEGRATING THE APPROACHES TO MENTAL DISEASE, Two Conferences Held under the Auspices of the Committee on Public Health of The New York Academy of Medicine, edited by *H. D. Kruse,* M. D. 393 pages. Paul B. Hoeber, Inc., Medical Book Dept. of Harper & Brothers, New York, N. Y. 1957. Price $10.

This is the well-edited report of two conferences in which leading exponents of the organic, experimental psychological, psychodynamic, and psychosocial approaches to understanding mental illness exchanged views in an effort to more clearly define areas of agreement and areas of disagreement, and to encourage research with broad objectives of integration of the various approaches. These worthy objectives, and the list of participants, doubtless led to unrealistic expectations on the part of this reviewer because the real value of such conferences can probably never be captured in print. The book contains brief expositions of the positions on etiology of mental disease of each of the four disciplines represented and a well-documented example of some of the difficulties to be overcome in the multidisciplinary approach to understanding the complex problem of human behavior. It will be of interest to anyone doing research in this field and worthy of careful study by those undertaking multidisciplinary evaluation of any aspect of the problem. —*MARION E. ROUDEBUSH, Capt., MC, USN*

TUMOR SURGERY OF THE HEAD AND NECK, by *Robert S. Pollack*, M. D., F. A. C. S. 101 pages; 112 illustrations on 49 figures. Lea & Febiger, Philadelphia, Pa., 1957. Price $5.

This book contains an interesting and practical approach to the diagnosis of head and neck tumors, diagnostic aids and procedures to be employed, and the argument of surgery versus irradiation therapy. In any discussion of radical head and neck surgery the final results as to the benefit to the patient are always to be considered and, as the author states, "operations on the medically indigent accomplish little in the way of positive results." In the author's presentation of preoperative basic concepts, it is obvious that a most intelligent and practical judgment has been used. This is not a basic surgical textbook nor is it intended to be such; however, the surgical technics that are explained throughout the entire text are most adequately described and shown. The reviewer agrees with the author about the term "recurrence." There is no doubt an entity of "recurrent cancer," however, as he states "residual" is most often the more correct term, and probably is due to the fact that considerable head and neck surgery is done by less fully trained surgeons. This is an excellent presentation of the basic principles of a most highly specialized type of surgery.

—*CLINTON S. LYTER, Col., MC, USA*

METHODS IN SURGICAL PATHOLOGY, by *Henry A. Teloh*, M. D. 127 pages. Charles C Thomas, Publisher, Springfield, Ill., 1957. Price $4.75.

There has been a need, for some time, for a manual of procedures for describing and processing tissue sent to a laboratory of surgical pathology. This is such a manual, and the author and publisher deserve commendation for making it available. It is compact, the print is good, the few illustrations are clear, and in general the contents are adequate. It was written primarily for resident trainees in surgical pathology and it will be very helpful to them. It is recommended for reading by surgeons also, particularly the discussions about frozen sections, the proper handling of specimens in the operating room, and the preferred gross sectioning technic if this is done before specimens are sent to the laboratory. The composition, unfortunately, is faulty. Awkward sentence construction and frequent and repetitious errors in grammar mar this otherwise worthy effort. The few references to the work of others should be completed.

—*WILMOT F. PIERCE, Capt., MC, USN*

BODY WATER IN MAN, The Acquisition and Maintenance of the Body Fluids, by *Maurice B. Strauss*, M. D. 286 pages; 31 illustrations. Little, Brown & Co., Boston, Mass., 1957. Price $7.

The virtue of this book lies not in the revelation of anything new, but in the collection of illustrative experiments and their organization into an orderly sequence to develop and verify the current theory of body water and the factors which control it. The chronological, historical approach is used both in the introductory chapters tracing the water adaptations of lower animals and within each of the later chapters dealing with specific factors such as thirst, renal water excretion,

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antidiuretic hormone, or aldosterone. The references are voluminous and will prove one of the major attractions to a student of the subject.

The scope of the book is broad and of necessity the narration is condensed. In some areas, such as the section on renal excretion of water, this brevity coupled with the special language and symbolism in vogue in this field makes it difficult reading for the uninitiated. It is doubtful if students or physicians not possessing this special background would profit much by it. A major general criticism, particularly in the renal section, is the failure to clearly differentiate, in the experiments quoted, between physiologic and unphysiologic conditions and mechanisms. For example, the statement is repeatedly made that drinking of sea water by castaways is not feasible because increased solute load lowers urine concentration and results in greater water loss. The experimental data supporting this conclusion all involve levels of urine flow greater than 5 cc per minute. At the lower rates to be expected of a castaway the relationship does not apply and the conclusion is not justified. In spite of these objections this is a worthwhile book and should be in the libraries of all teaching hospitals and those of individuals with a special interest in the field.

—*CHRISTIAN GRONBECK, Jr., Lt. Col., MC, USA*

THE GLAUCOMAS, by *H. Saul Sugar,* M. D., F. A. C. S. 2d edition. 516 pages; illustrated. Paul B. Hoeber, Inc., Medical Book Dept. of Harper & Brothers, New York, N. Y., 1957. Price $13.50.

This book, which is essential reading for ophthalmologists, expresses the authoritative current opinions on a major ocular problem. The subject is well organized and clearly written. Beginning with a brief historic review, glaucoma is discussed from an anatomical basis to the present broad divisions of narrow and wide angle glaucoma, secondary glaucoma, congenital and infantile glaucoma, and their respective possible etiological factors, pathogenesis, clinical symptomatology, diagnostic means, favored medical therapeutics, and surgical management. The bibliography is noteworthy, and the statistics cited are brief but significant. The preferred surgical procedure representing accredited and responsible concensus is well stated, a feature most valuable but found infrequently in writings on glaucoma. The author has wisely appealed to recognized authorities to incorporate their special contributions, thus further accenting the excellence of the contents. This reviewer enthusiastically endorses the book and extends congratulations to the author. —*RUDOLPH. P. NADBATH, Capt., MC, USN*

CHILD PSYCHIATRY, by *Leo Kanner,* M. D. With prefaces by *John C. Whitehorn,* M. D.; *Adolf Meyer,* M. D., LL. D.; and *Edwards A. Park,* M. D. 3d edition. 777 pages. Charles C Thomas, Publisher, Springfield, Ill., 1957. Price $8.50.

The third edition of *Child Psychiatry,* as in the previous editions, covers the field from every practical aspect and with encyclopedic thoroughness. Beginning with a chapter on the history of child psychiatry, the author follows through with basic orientations to include

chronological development, intelligence, emotional security, personality, parental attitudes, and the effect of material environment. He discusses the clinical considerations in the evaluation of the child, and the various forms of therapy both pharmacal and psychiatric. The greater portion of the book is devoted to personality problems arising from physical illness, psychosomatic problems, and those of behavior. There is a short but excellent section on childhood schizophrenia. This book is highly recommended to psychiatrists, neurologists, pediatricians, general practitioners, psychologists, and social workers interested in the problems of children and the diagnosis, care, and management of children with psychiatric conditions.

—*STEPHEN MOURAT, Lt. Col., MC, USA*

LABORATORY APPLICATIONS IN CLINICAL PEDIATRICS, by *Irving J. Wolman,* M. D. 1,019 pages. The Blakiston Division, McGraw-Hill Book Co., Inc., New York, N. Y., 1957. Price $15.

This excellent, comprehensive book should be of great value to the medical student entering his clinical years, the physician in residency training, as well as the general practitioner and pediatrician. It is not an exhaustive text of all detailed laboratory procedures, but stresses the intelligent choice and the proper evaluation of results in clinical pediatrics. The author emphasizes that the child is a separate entity from the adult not only clinically but in all aspects of laboratory studies. He points out that, with the rapid growth that takes place between birth and early adulthood, evaluation of abnormal laboratory findings and the changes in the normal values vary considerably during the progressive phases of growth.

The text is well written and readable. The concise but adequate bibliographies at the end of each chapter enhance the value of the work. This volume fulfills the mission for which it was probably intended, namely of being a reference book for handy consultation in a busy office practice or pediatric clinic rather than a formal text.

—*JOHN F. SHAUL, Capt., MC, USN*

MAY'S MANUAL OF THE DISEASES OF THE EYE For Students and General Practitioners, 22d edition, revised and edited by *Charles A. Perera,* M. D. 518 pages; 378 illustrations, including 32 plates with 93 colored figures. The Williams & Wilkins Co., Baltimore, Md., 1957. Price $6.

The twenty-second edition of this well-known standard textbook, as revised and edited by Doctor Perera, keeps faith in every detail with the aims that were outlined by Doctor Charles H. May when he published the first edition in 1900. It was his aim to present a concise, practical, and systematic manual on diseases of the eye for the use of the student and the general practitioner. This concept has been adhered to admirably. The familiar format remains the same with 26 chapters and 32 illustrations in colors. Each chapter, which deals with a separate part of the eye, begins with an excellent review of the anatomy concerned. This is one of the outstanding features of this book. There is no other textbook dealing with diseases of the

eye that adheres so devotedly to the presentation of subject matter without becoming involved in definitive detail. This book is so well known, because it is used as a standard text in a great many medical schools, that it needs no further recommendations. Suffice it to say, that it is a must on every doctor's shelf for ready reference.

—*AUBREY L. JENNINGS, Col., USAF (MC)*

MANUAL OF NUTRITION, 4th edition. Orginally written in Great Britain in 1945 by *Magnus Pyke*, Ph. D., F. R. I. C. 68 pages. Philosophical Library, Inc., New York, N. Y., 1957. Price $3.50.

The material in this manual is presented in an elementary form and would be instructive as a beginning text for self-study for those who work with foods but have no background in chemistry or physiology. Much more information would be gained if the material was presented by an instructor who was well informed in the science of nutrition. The volume contains a brief discussion of classes of nutrients, carbohydrates, fats, proteins, inorganic elements, and vitamins; digestion and absorption, energy requirements, recommended nutritional allowances, food composition, meal planning, and a very abbreviated table of food composition. Because it was designed primarily to meet the needs of the caterer it is difficult to understand the omission of any reference to the loss of nutrients through improper storage, preparation, and cooking practices. The essential amino acids are mentioned in the discussion on proteins but no mention is made of the essential fatty acids in the section on fats. Some of the texts listed at the end of the manual have appeared in later editions. —*ERNEST M. PARROTT, Lt. Col., MSC, USAR*

SURGERY OF THE BILIARY TRACT, PANCREAS & SPLEEN, by *Charles B. Puestow*, M. D., Ph. D. (Surg.) 2d edition. A Handbook of Operative Surgery. 381 pages; illustrated by *Jessie W. Phillips*. The Year Book Publishers, Inc., Chicago, Ill., 1957. Price $9.75.

The second edition of this fine monograph does not represent a major revision of the text. It has been brought up to date, however, by the addition of newer concepts and procedures, and by the deletion of material no longer considered of value. A new section on intravenous cholangiography has been added to emphasize the value of this diagnostic procedure in demonstrating the bile ducts in cholecystectomized patients. The utilization of body section radiography is included as a technic for sharpening the focus of intravenous cholangiograms by eliminating extraneous shadows. In the discussion of cholecystectomy it is advocated that clamps be placed on the cystic duct and artery, a practice which in this reviewer's experience has proved more hazardous than the ligation of these structures in continuity prior to their division. In the section on the pancreas several additional procedures for the surgical treatment of pancreatic disease have been added including the retrograde Roux-Y pancreaticojejunostomy for the relief of chronic pancreatitis as a method of decompressing the obstructed pancreatic duct. Interesting pancreatograms, through the distal transected duct, are illustrated and tend to confirm the author's belief that the stricture at

the proximal end of the duct often extends from 2 to 5 cm from the ampulla of Vater, a situation that would not be relieved by sphincterotomy.

One can find in this monograph an excellent description of the standard operations in this field and an ample account of the basic anatomy, physiology, diagnostic methods, and pre- and post-operative care. The line drawings are clear and the index adequate. This revised handbook is a fine guide to the education of surgical residents and as a reference work for the practicing surgeon.

—*JOSEPH J. ZUSKA, Capt., MC, USN*

GYNECOLOGIC AND OBSTETRIC PATHOLOGY, With Clinical and Endocrine Relations, by the late *Emil Novak*, M. D., and *Edmund R. Novak*, M. D. 4th edition. 645 pages; 683 illustrations, 25 in color. W. B. Saunders Co., Philadelphia, Pa., 1958. Price $14.

It is a sad note, indeed, that this fourth edition will be the last edition of the textbook on gynecologic and obstetric pathology under the name of Novak and Novak, due to the demise of the senior author. This news, however, is tempered by the request of the late Doctor Novak that Doctor Donald Woodruff, Chief of Gynecological Pathology at Johns Hopkins, will collaborate with the junior author in the preparation of future texts on this subject, which have been classical contributions to the medical profession.

The present text continues the same format as previous ones, with additions to the bibliography of the various sections, as indicated in bringing the text up to date. More thought has been given to the subject of basal cell layer hyperactivity and carcinoma-in-situ. In addition, Doctor John K. Frost, Chief of the Cytology Laboratory at Johns Hopkins Hospital and the University of Maryland, is the author of the chapter on recent cytologic developments, which is a valuable contribution to this text. Exfoliative cytopathology is still in its early developmental stage and not without diagnostic error. However, it is a tremendous valuable adjunct to other methods of diagnosis and treatment with emphasis toward earlier diagnosis and the important follow-up information, and other investigative data.

The section on breast pathology has been discontinued, which is a wise choice in view of recent modern texts delving into this subject alone.

Doctor Robert E. L. Nesbitt has taken the place of Doctor Louis Hellman and has revamped the section dealing with placental abnormalities, implantation, and placentation. There have been changes in some of the illustrations, most of which are superior.

The medical profession is fortunate in having this valuable text continued by two young specialists in this field who have been inspired by the senior author. This is a valuable text for the pathologist and the clinician in this specialty.—*HUMBERT L. RIVA, Col., MC, USA*

OPERATIVE OBSTETRICS, by *R. Gordon Douglas* and *William B. Stromme.* Foreword by *Nicholson J. Eastman.* 735 pages; illustrated. Appleton-Century-Crofts, Inc., New York, N. Y., 1957. Price $20.

The authors of this text have produced a book of great practical value for every physician who does obstetrics. It is written in a style that makes for easy reading, yet is not "wordy." Each facet of obstetrics is carefully treated in minute detail, complete with etiology, incidence, complications, and therapy, as well as expected prognosis. This information is "boiled down" to usable facts and technics that are valuable to all concerned, from the resident to the fully trained certified specialist in this field. It is also written with such practicability as to be invaluable to the general practitioner who is doing obstetrics. Each chapter is covered with a complete and carefully selected bibliography that makes further reference reading a relatively easy matter.

There is a reasonable amount of detail on each procedure, coupled with indications and contraindications of methods and results that may be expected. The latest practices in our outstanding clinics, methods of therapy, controversial ideas are freely discussed, without dogmatism—all of which makes this text very valuable as a reference for a teaching service as well as for an office. The chapter on the use of forceps is worth the price of the text alone. Prenatal, preoperative, and postoperative care are laid down with a usable clarity, that makes the text very valuable. Another helpful chapter is devoted to surgery "exclusive of the generative tract" and is worthy of repeated careful reading by all interested in the obstetrical field. The first 35 pages are devoted to a clear, concise review of pelvic anatomy and gives a splendid background for the rest of the book. It is obvious that this work evolved only after years of hard, careful study. It is a much needed volume and reflects great credit on its authors.

—*ROY W. TANDY, Sr., Capt., MC, USN*

ROOTS OF MODERN PSYCHIATRY, Essays in the History of Psychiatry, by *Mark D. Altschule,* M. D. 185 pages. Grune & Stratton, Inc., New York, N. Y., 1957. Price $5.75.

Dr. Altschule is widely known for his interest in physiologic psychology, and especially for his work on carbohydrate metabolism in brain disease. In this book he presents a series of essays on the history of psychiatry since the eighteenth century. At least one of the essays, that on "Ideas about Anxiety Held by Eighteenth Century British Medical Writers," appeared earlier in substantially the same form in the *New England Journal of Medicine* in 1953.

The book is interesting and the author has read extensively in the earlier literature. It is a curious book and, in a sense, it is history turned upside down. The recurrent thesis of the book is that "historical study . . . brings to light earlier criticisms of old ideas that apply perfectly well to the same ideas when they are propounded in modern language, and nearly as well to current ideas that are direct outgrowths of those used in the past." This is certainly true, provided that one

puts sufficient emphasis on the phrases "the same ideas," "nearly as well," and "direct outgrowths," and realizes their limiting significance. The psychiatry of the last two centuries has been predominantly a symbolic and dynamic psychiatry, and Altschule sees in its historic "failures" confirmation of its present inadequacy, and a spur to further exploration along physiologic lines.

In the ninth and concluding essay, "Greek Revival," Altschule flays Freud and "Freudism," and grossly overstates his case. It is immaterial, after all, whether the version of the Oedipus legend seized on by Freud is the "true" legend or merely one of a thousand different versions. One winces at repeated statements of Freud's "slovenly scholarship," and is aghast at the charge of his "poverty of invention." Nevertheless, these essays are thoughtful as well as thought-provoking, and deserve a wide readership.—*FRANK B. ROGERS, Lt. Col., MC, USA*

THE MICROBIAL WORLD, by *Roger Y. Stanier, Michael Duodoroff,* and *Edward A. Adelberg.* 682 pages; illustrated. Prentice-Hall, Inc., Englewood Cliffs, N. J., 1957. Price $8.

The authors, in presenting a modern synthesis of microbiological knowledge in a manner intelligible to the beginner, have produced a book which is easily among the best in the field. It should prove profitable to the beginner and instructive to experienced microbiologists. The text includes microbiological methods, microbial anatomy and physiology in considerable detail, the growth and death of bacteria, the major groups of microorganisms, mutation and gene transfer, evolution in bacteria, host-parasite relationships and chemotherapy, and the uses of microorganisms. A section entitled "The Biological Background," contains general biological facts considered essential for an appreciation of the study of the microorganisms. Perhaps the chief theme of the book is its emphasis on the role of microorganisms in the enrichment of the study of all living things. The authors excel in pithy expressions and simple, but elegant, analogies. For example, the meager nutrient requirements of the blue-green algae are epitomized as "pioneers in the biological colonization of the bleakest natural environment." The illustrations are excellent. The discussion of the precipitin reaction, for example, is elucidated by a diagram which shows how an excess of antigen or antibody may prevent the formation of antibody bridges. —*LOUIS H. MUSCHEL, Maj., MSC, USA.*

EAR, NOSE AND THROAT DYSFUNCTIONS DUE TO DEFICIENCIES AND IMBALANCES, by *Sam E. Roberts,* M. D. With a foreword by *Morris Fishbein,* M. D. 323 pages; illustrated. Charles C Thomas, Publisher, Springfield, Ill., 1957. Price $8.50.

The author lists such conditions as hypoglycemic states, vascular headaches, migraine, Meniere's disease, perceptive deafness, Hilger's syndrome, allergies, sinus dysfunctions, and hemorrhagic states in the aged, for which he proposes a system of treatment by correcting various imbalances. The imbalances may be nutritional, electrolytic, hormonal, and acid-base and insulin sugar in nature. His "basic

therapy" consists of dietary correction, vitamin and hormone supplementation, correction of insulin-sugar and acid-base imbalances, and also supplementation with potassium and calcium, and trace minerals, without overlooking other accepted therapies. An innovation is the promise by the author to revise certain dietary and instructional cards or charts as new knowledge becomes available, bringing the book up to date. Two of these are now available at an additional charge of one dollar, and are also convenient to furnish to patients.

There has been a large gap in our knowledge of the medical management of ear, nose, and throat disturbances, which is filled by this book. It could be read with profit by the ophthalmologists and pediatricians, as well as by the general practitioners. It is recommended reading for the medical officers, and should be used as a reference in our training programs, for lectures, and for residents.

—*LEROY L. KENNEY, Capt., MC, USN*

A TEXT-BOOK OF X-RAY DIAGNOSIS, by British Authors, in four volumes. Volume 1, in 5 parts: Central Nervous System; The Teeth and Jaws; The Eye; The Accessory Nasal Sinuses; The Ear and Temporal Bone. Edited by *S. Cochrane Shanks,* M. D., F. R. C. P., F. F. R., and *Peter Kerley,* C. V. O., C. B. E., M. D., F. R. C. P., F. F. R., D. M. R. E. 3d edition. 521 pages; 533 illustrations. W. B. Saunders Co., Philadelphia, Pa., 1957. Price $20.

This revised volume of a standard text provides a textbook and guide for those beginning the study of the skull and of neuroradiology. The book does not replace comprehensive reference texts because the authors presume that the reader is familiar with many of the fundamentals of neuroanatomy.

The first two chapters, which are concerned with technic and interpretation of plain films of the skull, are excellent and place this examination in its proper perspective. The comments on evaluation of suture separation, convolutional markings, and the pathogenesis of bone changes adjacent to intracranial tumor masses were particularly lucid. The radiographs which accompany the text are in the positive form and are poor in detail and contrast; however, they are supplemented by line drawings and by clinical photographs which clarify the film reproductions and the text. The chapters on ventriculography and arteriography cover these procedures in much detail including the technic used by the authors. The relative value of air study and arteriography is discussed and much concise clinical data are included.

The technical comments on myelography differ considerably from the standard procedures in American hospitals, particularly in regard to the indication for cisternal puncture and to nonwithdrawal of the contrast material after the examination is completed. This textbook is an asset to the radiologist's library and has sections in it of particular value to neurosurgeons and radiology residents. It provides an excellent key to the literature for those interested in further study of neuroradiology. —*JOHN A. ISHERWOOD, Col., MC, USA*

THE YEAR BOOK OF RADIOLOGY (1957-1958 Year Book Series). Radiologic Diagnosis, edited by *John Floyd Holt,* M. D., and *Fred Jenner Hodges,* M. D. Radiation Therapy, edited by *Harold W. Jacox,* M. D., and *Morton M. Kligerman,* M. D. 445 pages; illustrated. The Year Book Publishers, Inc., Chicago, Ill., 1957. Price $10.

This is an excellent compilation of abstracts of well-selected material from the literature for the period June 1956 to June 1957. The abstracts deal with every section of the human anatomy as to diagnosis and radiation therapy. Recent technical developments are mentioned. The editor's introductory comments concerning the controversial subject biologic hazards of diagnostic radiology are well worth consideration.

The book is well indexed for quick referral, both as to subject matter and as to authors. It is adequately illustrated. It is highly recommended to all radiologists who are anxious to keep up to date.

—*MALCOLM W. MASON, Capt., MC, USN*

PSYCHIATRY and the CRIMINAL, A Guide to Psychiatric Examinations for the Criminal Courts, by *John M. MacDonald,* M. D. 227 pages. Charles C Thomas, Publisher, Springfield, Ill., 1958. Price $5.50.

This book is an excellent, clearly written guide to the major problems of forensic psychiatry involving psychiatric evaluation prior to the institution of, or during criminal proceedings. It contains 16 chapters which are short and concise and offer an excellent practical survey of the problem of psychiatry and its relationship to criminal law. The chapters on the simulation of insanity, narcoanalysis and criminal law, amnesia, and epilepsy and the electroencephalogram, and their relationships to criminal law are particularly good; and those chapters dealing with the practical behavior of the psychiatrist as a witness in criminal proceedings are very valuable and can be recommended, particularly to the beginner who is new to court procedure.

There is a great deal of factual information in this little book, and excellent bibliographies may be found at the end of each chapter. The entire volume can be read in a few hours, and it contains sufficient information for most purposes to satisfy the major questions that occur in the psychiatric evaluation of criminals.

Doctor McDonald displays an excellent writing style in this book and very few criticisms can be made concerning the selection of material or his presentation of it. It is the feeling of this reviewer that the second chapter, dealing with tests of criminal responsibility, could be somewhat longer and more detailed. However, taken as a whole, one of the outstanding factors of the work is its brevity and conciseness, which results in a readable work on a subject which, to some people, appears dull and uninteresting. Perhaps this book will not have a great appeal to psychiatrists who spend a great deal of time in the court; however, to the average psychiatrist and student of psychiatry it will prove a very valuable addition to their personal libraries. —*ROY E. CLAUSEN, Jr., Lt. Col., MC, USA*

MEDICINE AND THE NAVY, 1200-1900, by *J. J. Keevil.* Introduction by Sir *Henry Dale.* Volume I—1200-1649. 255 pages; illustrated. Published by E. & S. Livingstone, Ltd., Edinburgh and London, 1957. Distributed by Williams & Wilkins Co., Baltimore, Md. Price $8.50.

This is the first volume of a projected history of medical care in the Royal Navy, although attention also is given to general nautical medicine. Starting with the Laws of Oleron, approved in 1194 by Richard the Lionhearted as the legal basis for the treatment of sick and injured seamen, the author has carried the story through to the early Stuart period. Of no small interest are the accounts of the "houses of pity" and other public and church hospitals that cared for not only the sailor but the "poor, blind, lame, sore, miserable, sick, and impotent people of the land."

With abundant references Dr. Keevil unfolds the gradual development of an organized medical service for the king's ships in peace and war. The part played by such men as John Woodall, the East India Company, the Barber Surgeons Company, and other medical groups is carefully described. The illustrations are well chosen and definitely add to the interest in the text. The book is authoritative and should be of interest not only to every naval surgeon but every naval officer or anyone with a liking for naval history. The volume is handsomely and appropriately bound in navy blue and gold and the typography is excellent. — *LOUIS H. RODDIS, Capt., MC, USN (Ret.)*

BONE TUMORS, General Aspects and an Analysis of 2,276 Cases, by *David C. Dahlin,* M. D. 224 pages; illustrated. Charles C Thomas, Publisher, Springfield, Ill., 1957. Price $11.50.

This excellent book is an analysis of 2,276 cases of bone tumor, unselected except for adequacy of material. The initial chapter, which is introductory and discusses the scope of the study, is followed by tables classifying the series, giving the distribution by histologic type and age of the patients, and the localization of the different tumors. The succeeding chapters discuss a specific tumor, except the final chapter which is devoted to conditions that commonly simulate primary bone tumors. The classification is based on that advocated by Lichtenstein.

Almost all of the chapters are identical in arrangement, a short generalized discussion being followed by a figure giving skeletal, age, and sex distribution of the subject tumor. This is followed by brief, concise information under the headings: incidence, sex, age, localization, symptoms, physical findings, roentgenologic features, gross pathology, histopathology, treatment, prognosis, and bibliography. Excellent black-and-white photographs depict the x-ray and pathologic features of the lesions. The book is well bound and printed on glossy paper in large, clear type. The wealth and availability of information and the excellent illustrations make this a highly useful book to those interested in bone tumors. —*HUGH B. HOEFFLER, Lt. Col., MC, USA*

ANNALS OF THE NEW YORK ACADEMY OF SCIENCES, Volume 68, Art. 2, Pages 245-656, October 21, 1957, editor-in-chief, *Otto V. St. Whitelock.* "Subcellular Particles in the Neoplastic Process." Consulting Editor, *Cornelius P. Rhoads.* 411 pages; illustrated. The New York Academy of Sciences, New York, N. Y., 1957. Price $5.

This paper-bound volume is a collection of 28 papers presented at a conference under the auspices and at the New York Academy of Sciences on November 19 and 20, 1956. It is a complex, detailed, and highly technical report of the viral, bacteriologic, immunologic, genetic, and pathologic aspects of the etiology of cancer. The increasing recognition of the etiologic role of the viruses in neoplastic diseases is emphasized by the attention given to three diseases of virus origin (viral lymphomatosis of the chicken, rous sarcoma of the chicken, and mammary cancer of mice). An array of data is presented demonstrating the infectiousness and transmissibility of these viruses and the various modifying influences of hormones, chemicals, and immunizing agents on the host animals. Study of this volume is, of course, a necessity for the investigator in cancer etiology; for the clinician, a perusal of it can be an inspirational and rewarding experience. —*ROALD N. GRANT, Capt., MC, USN*

THE CLOSED TREATMENT OF COMMON FRACTURES, by *John Charnley,* B. Sc., M. B., F. R. C. S. 2d edition. 259 pages; illustrated. The Williams & Wilkins Co., Baltimore, Md., 1957. Price $10.

In this second extensively revised edition, the author has very successfully championed the case for closed treatment of fractures. The book is roughly divided into two major portions. The initial chapters cover some of the general factors involved in fracture healing and, based upon them, the author presents mechanical principles necessary for uncomplicated fracture healing. He emphasizes throughout the importance of the periosteum and its necessary part in the reduction and subsequent healing. The second portion of the book deals with methods of closed reduction and management of specific fractures. Nothing is left to the imagination, and herein lies the major value of the book. Such details as the placement of the operator's and assistant's hands, and the utilization throughout the manipulation of forces applied are described and illustrated. The pitfalls inherent in each reduction are indicated and the common error of too frequent post-reduction plaster changes is noted.

This book cannot be considered, nor was it meant to be, a definitive work on fracture management. It is, however, an excellent supplement to other more comprehensive volumes and will be most useful to the orthopedic and general surgical resident. In addition, there are many helpful suggestions that will be welcomed by the more experienced fracture surgeon. The emphasis on conservative principles, the concise descriptions and illustrations of closed manipulative reductions, and sound methods of post-reduction management, all recommend this manual of fracture treatment. —*STERLING J. RITCHEY, Col., MC, USA*

CLINICAL PATHOLOGY DATA, compiled by *C. J. Dickinson,* B. A., B. SC., B. M., M. R. C. P. With a foreword by *C. E. Dent,* Ph. D., M. D., F. R. C. P., F. R. I. C. 2d edition. 91 pages. Charles C Thomas, Publisher, Springfield, Ill., 1957. Price $4.

"This is not a textbook. It is a book for quick reference to the problems which a doctor meets when interpreting laboratory investigations. Normal values are given together with most of the known alterations in disease. The book does not pretend, and is not intended, to *teach* clinical pathology, for it assumes in the reader knowledge enough to approach the subject with a proper sense of proportion."

The above is taken from the cover of the book and adequately explains the nature of this text. This new edition is more comprehensive than the first edition and has sections dealing with the adrenal, liver, renal function tests, serologic tests for syphilis, and porphyrin metabolism. It is unfortunate that the author, in his own introduction, apologizes for having written the book, but as he has stated, "I still believe there is a place for a book of this sort." One must remember that the results in a laboratory do not always conform to the normal ranges as may be given in a text of this kind. The interpretations will assist a clinician who has too little time to do his own reading. This volume certainly should not be used as a textbook for students.

—JOE M. BLUMBERG, Col., MC, USA

Selected Writings of WALTER E. DANDY, compiled by *Charles E. Troland,* M. D., and *Frank J. Otenasek,* M. D. 789 pages; illustrated. Charles C Thomas, Publisher, Springfield, Ill., 1957. Price $15.

It is not often that one man makes several significant contributions in the field of medicine. Walter Dandy was one of these rare individuals and this group of collected papers gives in chronological order not only the evidence for these contributions, but also highlights the history of modern neurosurgery. Doctor Dandy's articles are on such varied subjects as the mode of absorption of spinal fluid, the demonstration of intracranial space-occupying lesions by injection of air into the lumbar subarachnoid space or the cerebral ventricles, total removal of tumors of the eighth cranial nerve in the cerebellopontine angle, subtotal section of the fifth nerve at the pons for tic douloureux, recognition and surgical removal of herniated nucleus pulposus, and the planned intracranial attack upon vascular aneurysms of cerebral blood vessels. These articles are guideposts to more intelligent, safer, and comprehensive surgical treatment of disorders of the central nervous system.

There are 78 papers presented in this volume, all of which are interesting. It is regretted that the editors did not include a biographic sketch of Doctor Dandy, although in truth careful perusal of the works gives a good idea of the man himself. Also, there are a number of typographical errors in the book. This volume should be the prized possession of anyone practicing or planning to practice neurosurgery and should be in every institutional medical library.

—GEORGE J. HAYES, Lt. Col., MC, USA

PRACTICAL ELECTROCARDIOGRAPHY, *Henry J. L. Marriott,* M. D. 226 pages; illustrated by *Marcie Ethride Perry.* 2d edition. The Williams & Wilkins Co., Baltimore, Md., 1957. Price $5.

This book, which describes abnormal electrocardiograms and the mechanisms involved in their production, has been thoroughly revised in keeping with the changing concepts. More illustrations have been added. The usual long and often tiring discussion of dipole theories, vectors, and gradients is omitted. The author proceeds directly with the discussion of tracings and patterns in a logical and direct sequence. He believes that interpretation of electrocardiographic tracings should be kept simple and not made to appear mysterious and difficult. This point is brought home with this book. Review tracings at the end of some chapters help the reader to note his progress. The volume is of most value to the beginner in electrocardiography, the medical student, intern, or young resident. It serves as an excellent review for all who need brushing up on occasion. The general practitioner and internist will find it most helpful in his library to assist in interpretation of tracings. —*WILLIAM R. SCHILLHAMMER, Maj., MC, USA*

PROGRESS IN NEUROLOGY AND PSYCHIATRY, An Annual Review, Volume XII, edited by *E. A. Spiegel,* M. D. 657 pages. Grune & Stratton, Inc., New York, N. Y., 1957. Price $12.

This is the twelfth of a series of annual reviews of the progress of neurology and psychiatry, edited by Dr. E. A. Spiegel, Professor and Head of the Department of Experimental Neurology, Temple University School of Medicine. This book covers a review of the literature of the previous year and is divided into four sections, all written by different authors: (1) 5 chapters on basic sciences, (2) 10 chapters on neurology, (3) 6 chapters on neurosurgery, and (4) 12 chapters on psychiatry. It is probably of some significance that 400 of the 643 pages are devoted to basic sciences, neurology, and neurosurgery. Reviews of this type are necessarily sketchy; however, for the most part, the chapters seem to be well done.

This book is a ready source of recent reference material and will be of great value to the teacher in neurology and psychiatry, and to the student. The approach is somewhat different from that of the annual *Yearbook of Neurology, Neurosurgery and Psychiatry* in which articles are reviewed but in somewhat more detail. Extensive and complete bibliographies are provided at the end of each chapter. The chapter on epilepsy, for example, though only 10 pages long includes 176 references on the subject. It is the opinion of this reviewer that this volume is well worth the purchase price to the specialist or to the student in neuropsychiatric subjects. A minor drawback noted throughout the book is a rather unusual number of typographical errors. It is the feeling of this reviewer that this book deserves a continued place in the annual literature of neurology and psychiatry, and that it fills a definite need for busy clinicians and workers in the field who wish a rather complete general survey of the year's literature.

—*ROY E. CLAUSEN, Jr., Lt. Col., MC, USA*

CIBA FOUNDATION COLLOQUIA ON ENDOCRINOLOGY, Volume 11, HORMONES IN BLOOD. Editors for the *Ciba Foundation: G. E. W. Wolstenholme*, O. B. E., M. A., M. B., B. Ch., and *Elaine C. P. Millar*, A. H.-W. C., A. R. I. C. 416 pages; illustrated. Little, Brown & Co., Boston, Mass., 1957. Price $9.

This volume contains the proceedings of the 17th Endocrinological Conference sponsored by the Ciba Foundation. It is devoted primarily to the detection, assay and transport of hormones within the blood. The reports dealing with the assay methods for pituitary, adrenal, and thyroid hormones are concise and well edited. The chapters on hormone transport are enlightening. Though the colloquia is primarily concerned with laboratory technics and research, there are many observations presented which will ultimately be of clinical significance. The participants in the symposium are prominent investigators in endocrinology and the reader will be interested in the discussions which have been presented after each paper. These comments are pertinent and reflect current knowledge and future paths for research in the study of hormones. Research workers and students in the field of endocrinology will find this book of inestimable value. However, it offers little for the practitioner.—*JOSEPH H. AKEROYD, Lt. Col., MSC, USA*

THE DIAGNOSIS AND TREATMENT OF INFECTIONS, by *D. Geraint James*, M. A., M. D. (Cantab.), M. R. C. P. (Lond.) 234 pages. Charles C Thomas, Publisher, Springfield, Ill., 1957. Price $6.

This book is an attempt to correlate the clinical and laboratory aspects of present-day treatment of infections. It is divided into three parts. The first part discusses current chemotherapeutic agents regarding their antimicrobial range, indications for use, their fate in the body and complications resulting therefrom. Part 2 is a discussion of the micro-organisms responsible for human infections, while Part 3 discusses infections of systems.

There is the inevitable overlap inherent in such types of presentation with a little information on certain aspects under discussion, followed later by some repetition and more detailed presentation in another section. This requires frequent cross reference and necessitates skipping from section to section for an adequate total picture of the problem at hand.

It was noted in some discussions on therapy of specific diseases that dosage schedules are not entirely in keeping with those recommended by American authors, *e. g.*, the intermittent dosage schedule of streptomycin in tuberculosis is not mentioned. It was also apparent in several specific diseases that dosages of drugs are somewhat lower than these generally accepted in this country.

Except as a quick reference regarding the more recent broad-spectrum antibiotics relating to their mode of action, range of activity, laboratory data and complications, this book does not fit any special need of the average general practitioner or specialist in this country. It would have limited value for interns.

—*JULES J. McNERNEY, Lt. Col., MC, USA*

New Books Received

Books received by the *U. S. Armed Forces Medical Journal* are acknowledged in this department. Those of greatest interest will be selected for review in a later issue.

PEDIATRIC CLINICS OF NORTH AMERICA, February 1958, Symposia on: Gynecologic Problems, *Goodrich C. Schauffler,* M. D., Consulting Editor, and Pediatric Ophthalmology, *Harold G. Scheie,* M. D., Consulting Editor. 255 pages; illustrated. W. B. Saunders Co., Philadelphia, Pa., 1958. Price $15 per year of four numbers (February, May, August, November).

THE PRACTICE OF INFECTIOUS DISEASE, by *Louis Weinstein,* Ph. D., M. D. 501 pages. Landsberger Medical Books, Inc., New York, N. Y. Distributed by The Blakiston Division of the McGraw-Hill Book Co., New York, N. Y., 1958. Price $8.50.

A. M. A. SCIENTIFIC EXHIBITS, 1957, sponsored by *Council on Scientific Assembly, American Medical Association.* 480 pages; illustrated. Grune & Stratton, Inc., New York, N. Y., 1957. Price $15.

CARDIOVASCULAR COLLAPSE IN THE OPERATING ROOM, by *Herbert E. Natof,* M. D., and *Max S. Sadove,* M. D. Foreword by *Warren H. Cole,* M. D. 197 pages; illustrated. J. B. Lippincott Co., Philadelphia, Pa., 1958. Price $6.

GENERAL PATHOLOGY, based on Lectures delivered at the Sir William Dunn School of Pathology, University of Oxford, edited by Sir *Howard Florey.* 2d edition. 932 pages; illustrated. W. B. Saunders Co., Philadelphia, Pa., 1958. Price $16.

CLINICAL INTERPRETATION OF LABORATORY TESTS, by *Raymond H. Goodale,* M. D. 4th edition. 758 pages; 105 illustrations, 6 in color. F. A. Davis Co., Philadelphia, Pa., 1958. Price $8.75.

PRACTICAL PEDIATRICS, by *R. Cannon Eley,* M. D., and *Benjamin Kramer,* M. D. 307 pages. Landsberger Medical Books, Inc. Distributed by The Blakiston Division of McGraw-Hill Book Co., New York, N. Y., 1958. Price $7.

A THERAPY FOR ANXIETY TENSION REACTIONS, by *Gerhard B. Haugen,* M. D.; *Henry H. Dixon,* M. D.; and *Herman A. Dickel,* M. D. 110 pages. The Macmillan Co., New York, N. Y., 1958. Price $3.50.

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